Twenty-Third Annual Meeting
New York City, May 29-June 2, 1957

VOLUME XXXI NUMBER 2

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

AMERICAN COLLEGE OF CHEST PHYSICIANS

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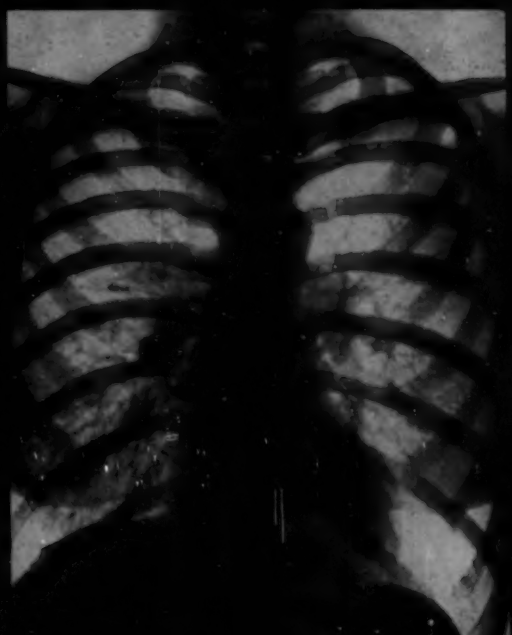
Bronchogram of right lung with VISCIODOL. Note clear outline of bronchi and absence of alveolar filling.



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1. Burrascano, J. J.: Sea View Hosp. Bull. *15*:149 (July) 1955.

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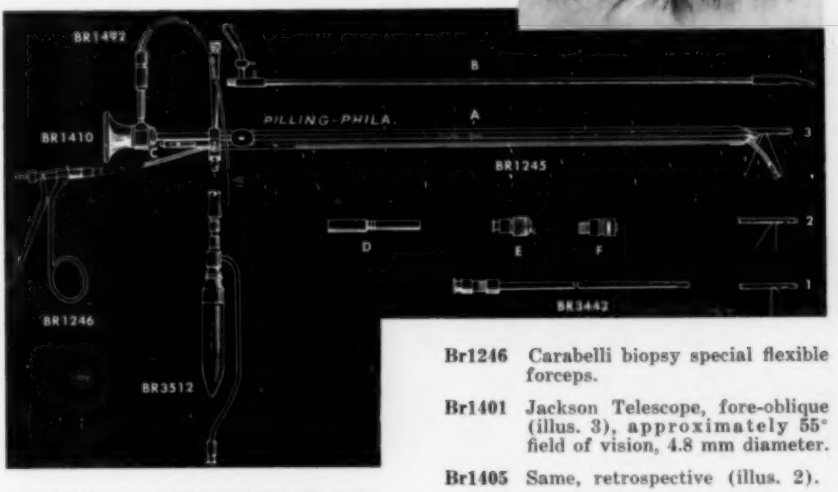

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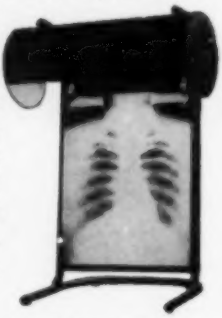

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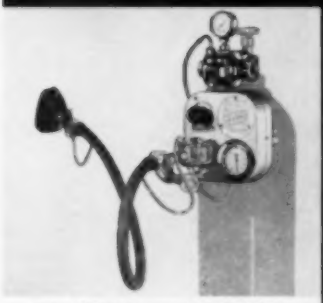

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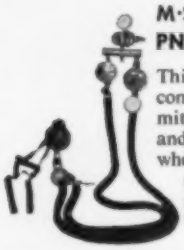

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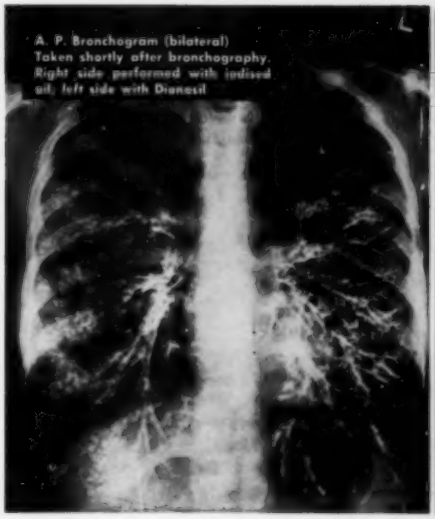

A. P. Bronchogram (bilateral)
Taken shortly after bronchography.
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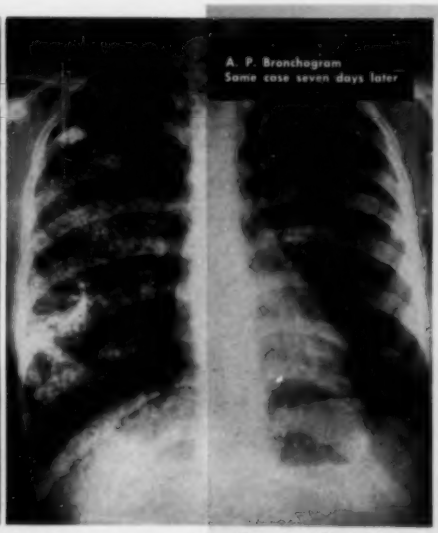

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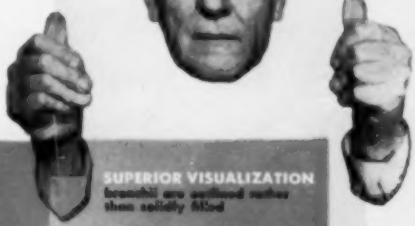

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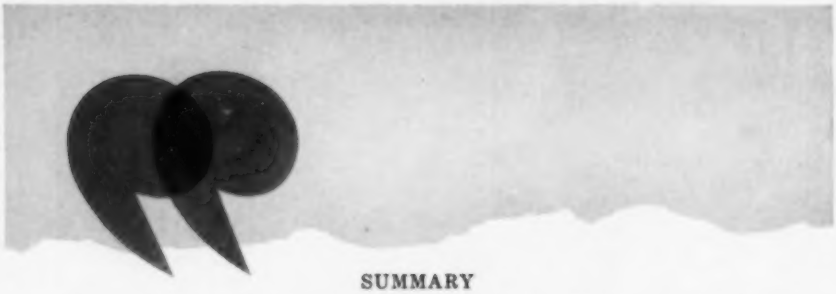

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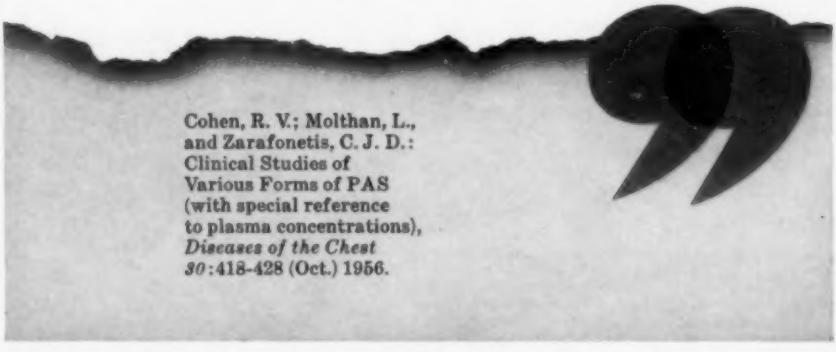

Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* *30*:418-428 (Oct.) 1956.

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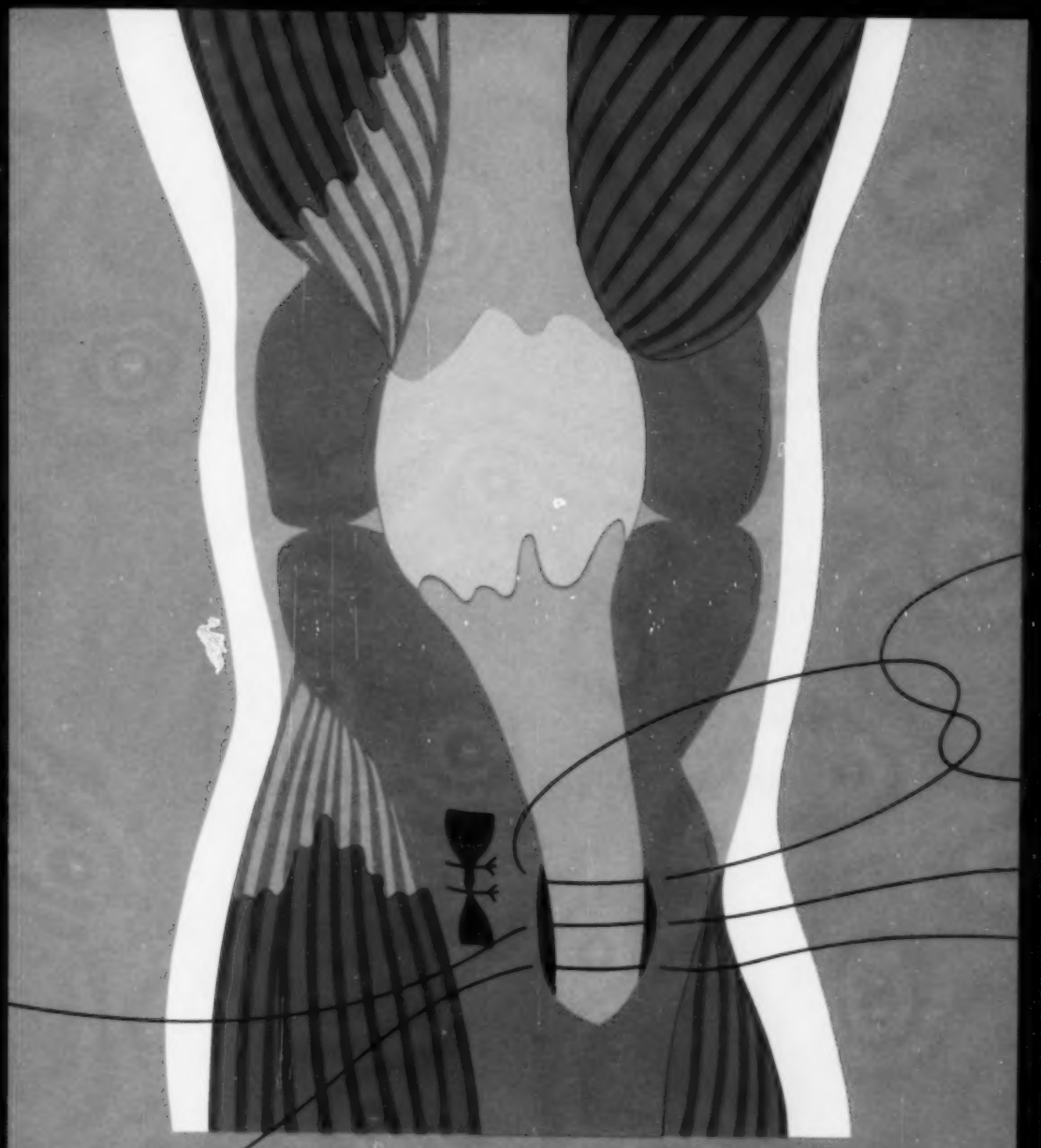

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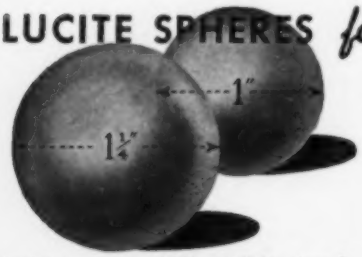

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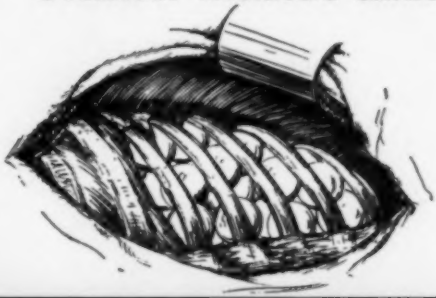

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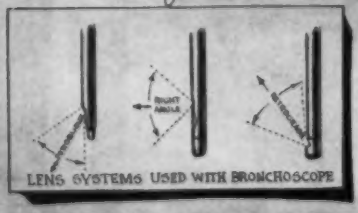

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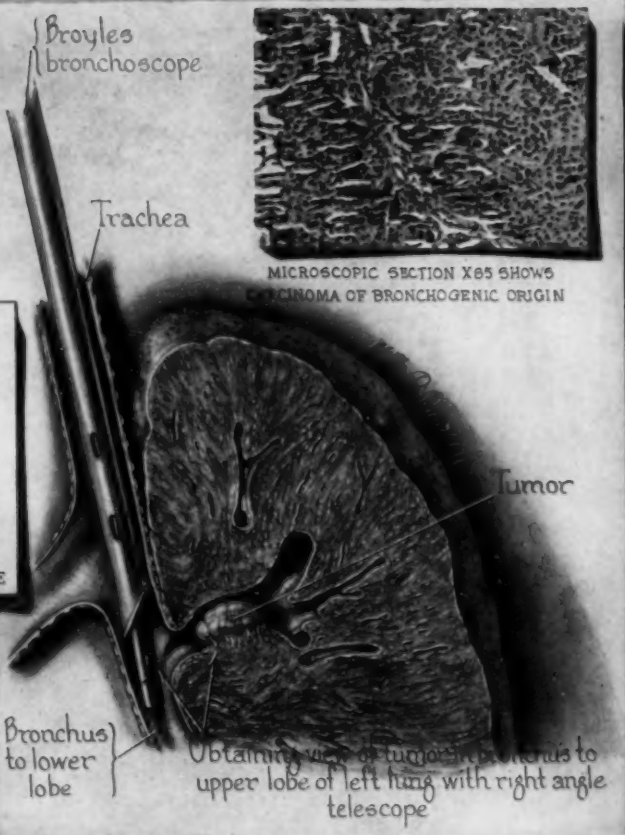
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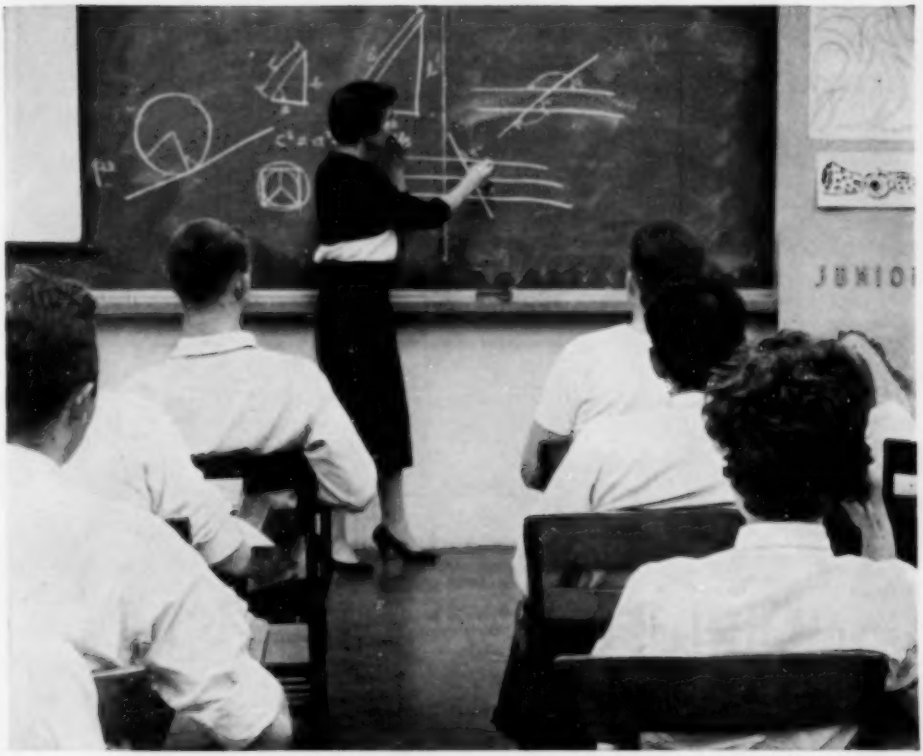

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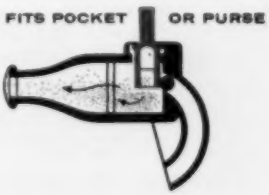

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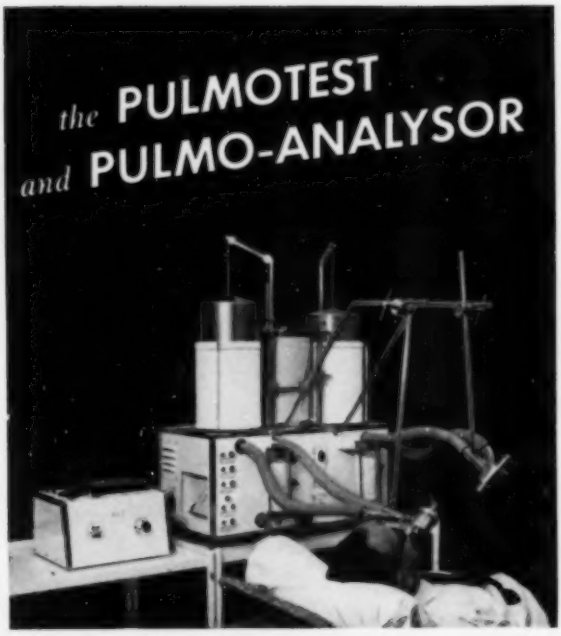

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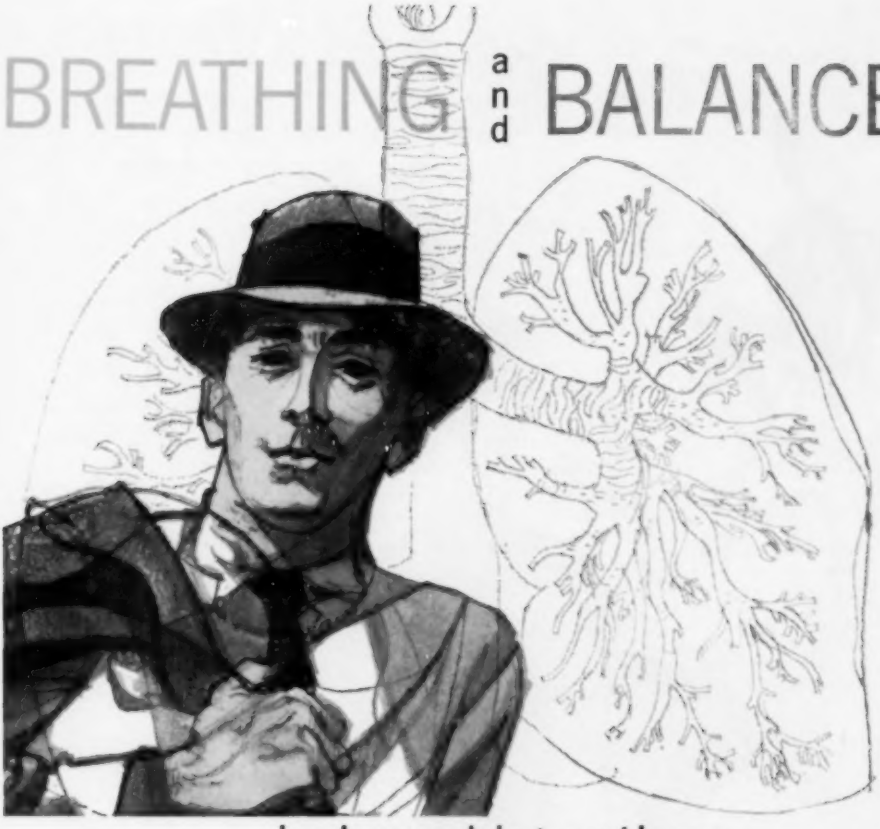

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*Schwartz, E.: New York J. Med. 56:570, 1956.

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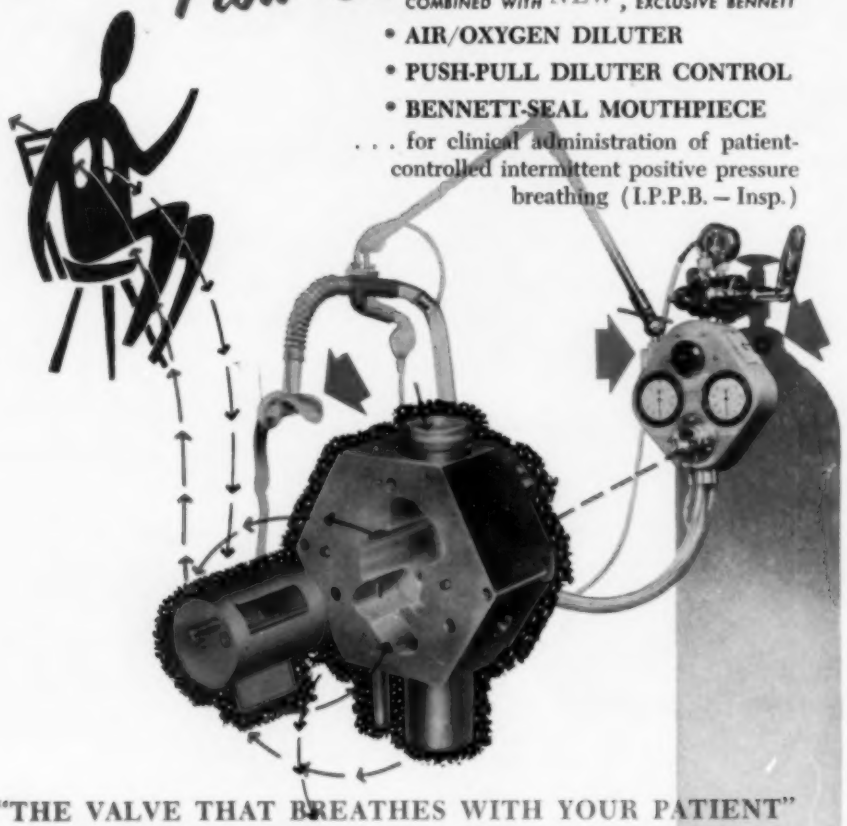

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DISEASES of the CHEST

VOLUME XXXI FEBRUARY, 1957 NUMBER 2

Pulmonary Function Testing

A Special Exhibit from the Section on Diseases of the Chest of the American Medical Association*

GEORGE R. MENEELY, M.D., F.C.C.P.*

Nashville, Tennessee

DEFINITION OF OBJECTIVES

Practical Pulmonary Function Testing

Planning a pulmonary function testing program:

There is as much need in the modern hospital for a lung station as there is for a heart station and one can be staffed and equipped at no greater expense than the other. A clear definition of objectives is essential. Consideration must be given to what tests of function can and cannot do and the real professional, technical, physical, and financial resources available.

The common denominator among patients referred for pulmonary function testing is that they have or are suspected of having chronic pulmonary disease. The general purpose of pulmonary function testing is to detect impairment and if present, to characterize it and estimate its severity. The specific purpose derives from the nature of the problem which the particular patient presents to his doctors or to interested third parties such as insurance companies, employers or compensation boards. A routine suitable for one purpose may not serve another although certain tests should probably be employed in every case.

There is often a lack of awareness that some of the outstanding laboratories from which emanate a large fraction of the important publications in the field are primarily research organizations which, despite a large staff, a heavy investment in equipment and a generous operating budget can actually work up only a few patients each week. In a laboratory organized to provide a clinical service, close attention must be given to the versatility of each instrument, the level of technical skill required to operate it and the amount of time involved in each test. In the long run, personnel becomes the major budgetary item and efficiency is at a premium. Often a larger investment in equipment is justified by the rapidity or facility with which individual tests can be performed.

Real resources available:

The traditional approach to the problem of pulmonary function testing is to develop a schema of the respiratory processes and then review methods available for testing each component. However desirable this may be for teaching purposes, it does not answer the practical question. Laboratory activities are circumscribed by instrumental resources and the skill and available time of the medical and technical staff. Tests of pulmonary function can be classified horizontally by purpose and vertically by degree of complexity, equipment required and extent of experience needed to perform them. It is logical, therefore, to approach the problem by reviewing the instruments which have been found generally useful and analyzing what can be accomplished with them. Then, with the particular objectives clearly outlined, it should be possible to select the equipment which most nearly fits the requirement, set up the desired methods and operate an effective lung station within the framework of the available real resources.

There is now fairly general agreement on "basic" equipment and methods. The irreducible minimum procedure which can be termed a test of pulmonary function is the determination of timed vital capacity; i.e., one second, three second and total vital capacity and total vital capacity time. Relatively simple equipment suffices and the procedure is suitable for office work as well as in the small hospital

*Chairman, General Committee, Special Exhibit on Pulmonary Function Testing, American Medical Association.

Copyright, 1957, by the American College of Chest Physicians

or clinic. Closed circuit respirometry with a well constructed low resistance two speed recording respirometer with ventilograph is certainly the next step. This versatile instrument is also practical for office work by men particularly interested in chest disease. Next in order is determination of arterial oxygen saturation and carbon dioxide content. The basic method today employs the Cournand needle, syringe sample storage and analysis with the manometric Van Slyke apparatus. Other methods are promising but have not stood the test of time.

When this procedure is available, it is highly desirable to add arterial pH determination with a modern simple direct glass electrode blood pH meter. Next, determination of the lung volume and its fractions is widely accepted as the best measure of the degree of pulmonary distention present and of special value in the appraisal of pulmonary emphysema, but agreement is less general about methodology. All of the methods in current use give values which are useful clinically. Whether bronchospirometry is included in the "basic" repertoire will depend upon the specific purpose of the program and is most generally useful in pre- and post-operative evaluation of thoracic surgery patients.

There are a large number of procedures which are "on the way" from the research laboratory to the clinic. The extent to which the basic repertoire may be expanded is limitless but contemplated additions should be considered carefully in terms of their established value and the instrumental and time investment required.

This presentation is primarily confined to actual tests of pulmonary function but three important collateral matters must be considered. First, fluoroscopy is of such importance in all aspects of chronic pulmonary disease that it must be assumed a fluoroscope is available and that the doctor responsible for function testing personally fluoroscopes each patient as an integral part of the routine. Second, close integration of the clinical cardiac and respiratory laboratory program is always desirable and particularly so if advanced procedures are to be employed because there is a large overlap of methodology. Efficient and economical utilization of skilled personnel and elaborate equipment dictates adjacent physical location or even actual combination if wasteful duplication of equipment and technical skills is to be avoided. There are, of course, circumstances which may require separate establishments but in any event, cooperation and close integration are invaluable. Third, the training and experience of the doctor responsible for the testing program may dictate selection of particular methods because of personal familiarity with them and confidence in them.

What pulmonary function tests can do:

1. Provide the information needed for an *objective* appraisal of pulmonary impairment, insufficiency or disability when interpreted in relation to the other findings in the patient. Extensive involvement of the lungs seen in x-ray shadows may be associated with little or no pulmonary impairment while others with little roentgenological evidence of disease may have true pulmonary disability.
2. Useful in ruling out pulmonary disease in non-organic types of dyspnea such as psychoneurosis, neurocirculatory aesthenia, etc.
3. May provide a quantitative measure of pulmonary function which can aid in the evaluation of candidates for permanent forms of collapse therapy or surgical removal of lung tissue, both so far as immediate risk and ultimate useful existence are concerned.
4. May aid in following objectively certain aspects of the course of pulmonary disease.
5. May permit evaluation of therapeutic measures, medical or surgical.
6. Aid in differentiating cardiac from pulmonary disease.
7. Aid in differentiating primary from secondary types of polycythemia.
8. Occasionally permit detection of pulmonary abnormalities in patients in whom physical examination and x-ray studies cannot disclose certain diseases of the lung.
9. May be useful in pre-employment evaluation.
10. Aid in evaluation disability claims in insurance or industrial practice.
11. Pulmonary function studies indicate the specific function of the lung that has been impaired by disease and give the physician a clearer concept of the disease process in each patient.

What pulmonary function tests cannot do:

1. Cannot provide etiological or anatomical diagnoses but only physiological diagnoses, estimates of functional capacity and, sometimes, information of prognostic import.
2. Cannot localize a process geographically: thus certain tests might reveal the existence of a venous-arterial shunt but in themselves fail to identify it as intracardiac or intra-pulmonic.
3. Cannot distinguish between processes

producing certain effects; for example, impaired diffusion across the alveolo-capillary membrane might be demonstrated but without distinguishing between alveolar edema and interstitial edema.

4. Cannot reveal pulmonary disease unless function is impaired and then only when impairment is of sufficient degree that present tests can recognize with certainty the deviation from normal values; thus slight reduction in function cannot be detected nor involvement of small areas only.
5. Localized disease produces changes only when so much space is occupied or the lesion is strategically situated so that function is affected. As with other parenchymatous organs, diffuse disease is far more likely to impair function than localized lesions.
6. Cannot supplant careful analysis of the history, physical examination, fluoroscopic and other radiological examinations, bacteriological or pathological studies.
7. No single test now known is sufficient for evaluation of all aspects of pulmonary function.
8. At present sufficient data have not been obtained upon large enough groups of *healthy* persons to determine with certainty w at constitutes normal values for pulmonary function in men and women of all age groups and what values represent an irreducible minimum below which patients cannot live in comfort.

Methodology

Resources from the instrumental point of view:

A. *Closed circuit equipment*

1. *Vital capacity spirometer with timing device:*

   Timed VC, total VC, total VC time.

2. *Two speed respirometer with ventilograph:*

   The above plus: f, TV, ERV, IC and MV at rest, during exercise, and maximal voluntary effort, patterns of the respiratory tracing, O_2 consumption (during steady states only), ORR, BMR, BR and BR/MBC.

3. *Respirometer as in 2. with helium analyzer added:*

   The above plus: FRC, RV, TC and RV/TC. If circuit with blower is used, intrapulmonary mixing can be measured.

B. *Open circuit equipment:*

1. *Simplest version: low resistance breathing valves, Douglas bag and valve, gas meter and stop watch.*

   F, TV and MV at rest, during exercise and maximal, BR, BR/MBC.

2. *Tissot spirometer* (used direct or to measure volumes transferred from bags. A kymograph is useful. More precise than gas meter.) Observations same as 1.

3. *Either 1. or 2. with provision for gas analysis, switching to 100% O_2 and collecting Haldane-Priestly "alveolar air" samples.*

   Same as 1. and 2. plus O_2 consumption, ORR, FRC, IIM. (For lung volume, ERV, IC, etc. must be determined with a closed circuit respirometer.)

C. *Van Slyke manometric apparatus:*

Analysis of arterial blood samples for O_2 saturation and CO_2 content (and many other analyses).

D. *Glass electrode blood pH meter:*

Arterial pH, (and, with CO_2 content known, arterial CO_2 tension).

DEFINITIONS RELATING TO PULMONARY FUNCTION

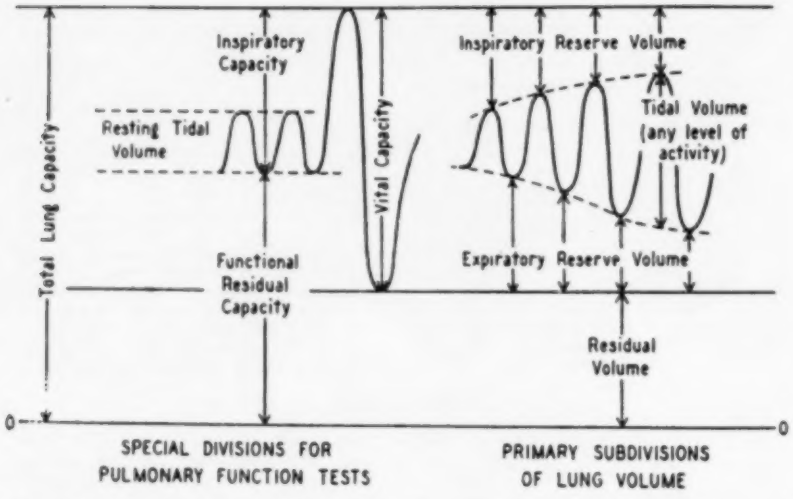
"Standardization of Definitions and Symbols in Respiratory Physiology"

(Abridged from Federation Proceedings, Vol. 9, Pages 602-605, 1950)

"On April 19, 1950, a group of physiologists met in Atlantic City to discuss the possibility of establishing a systematic set of symbols for use in teaching and research publications relating to respiratory physiology. The need for such a set of symbols is great . . .

"The following definitions and symbols represent the fruit of these discussions and they are presented here with the hope that authors and editors will use them as a reference source to achieve uniformity and clarity in terminology in the field of respiratory physiology . . .

"The following have agreed to follow the above terminology and system of notation wherever possible in their future teaching and research publications: J. H. Comroe, University of Pennsylvania, A. Cournand, Columbia University, J. K. W. Ferguson, University of Toronto, G. F. Filley, Trudeau Foundation, W. S. Fowler, University of Pennsylvania, J. S. Gray, Northwestern University, H. F. Helmholtz, Jr., Mayo Clinic, J. R. Pappenheimer (Chairman), Harvard University, H. Rahn, University of Rochester, R. L. Riley, New York University."



Subdivisions of the Lung Volume—All gas volumes corrected to body temperature, pressure and saturated with water vapor BTPS.

Definitions of lung volume are shown diagrammatically above. The "volume" subdivisions shown at right apply to all levels of respiratory effort and contain no overlapping volumes. The "capacity" terms at left each include two or more primary "volumes" and are specially convenient for clinical applications where gasometric measures are most simply made from the expiratory position of the resting patient.

Usual Abbreviations and Definitions of Terms: (The Pappenheimer committee recommendations are followed as closely as possible for clinical purposes.)

Lung Volume:

TV: Tidal Volume: volume, BTPS, of each breath.

ERV: Expiratory Reserve Volume: volume, BTPS, expelled by maximal effort beginning at end of normal expiration.

IC: Inspiratory Capacity: volume, BTPS, inspired by maximal effort beginning at end of normal expiration.

VC: Vital Capacity: a) *one stage:* volume, BTPS, expelled by maximal expiratory effort beginning at end of maximal inspiratory effort. b) *two stage:* sum of IC plus ERV determined separately.

RV: Residual Volume: volume, BTPS, remaining in lung at end of maximal expiration.

FRC: Functional Residual Capacity: volume, BTPS, remaining in lung at end of normal expiration.

TC: Total Lung Capacity: volume, VTPS, in lung at end of maximal inspiration.

Essential Information

State of the Patient: i.e., during an attack of asthma, etc.

Position of the Patient: i.e., supine, etc.

Activity of the Patient: i.e., resting, exercise, etc.

Corrections Applied: Observations are usually corrected to some standard condition:

STPD: Standard conditions of temperature and pressure, dry. (0° centigrade, 760 mm. Hg. barometric pressure)

BTPS: Normal body temperature, ambient pressure, saturated with water.

ATPS: Ambient temperature and pressure, saturated with water.

Relation of Observations to Normal Standards:

"Normal" values for a particular patient are often *predicted* from tables, graphs or equations based upon height, weight, age, sex, etc. An observation may be expressed as a *percent of the Predicted value (% Pred.)* or as a *percent Difference (% Dif.)* from the predicted value.

Definitions

Respiration: The gaseous exchange between an organism and its environment.

Internal Respiration: The exchange of gases between tissue cells and the fluid bathing these cells.

External Respiration: The exchange of gases between the blood and air entering the lung.

Mechanisms of External Respiration:

1. *Ventilation:* The movement of air in and out of the lungs.
2. *Mixing:* The intrapulmonary mixing of the Respiratory gases.
3. *Diffusion:* The exchange of oxygen and carbon dioxide across the alveolocapillary membrane.
4. *Perfusion* (Circulation): The quantity and distribution of blood flow through the lungs.

Impairment: Significant deviation from normal.

Insufficiency: Failure to meet normal requirements for ordinary activity or abnormal compensation to meet normal requirements.

Disability: The individual is rendered incapable of meeting the requirements of ordinary activity.

Ventilation Studies:

f: Respiratory *frequency* (rate).

M: Maximal and per *Minute.*

MV: Minute Ventilation.

MMV=MBC: Maximal Minute Ventilation=Maximal Breathing Capacity.

BR: Breathing Reserve: (VR: Ventilatory Reserve:) MBC minus resting MV.

BR/MBC x 100: Ratio of Breathing Reserve to *Maximum Breathing Capacity,* per cent.

ORR: Oxygen Removal Ratio: ml. 0_2 consumed per liter ventilation.

VE: Ventilatory Equivalent: liters ventilated per 100 ml. O_2 removed. (Note that VE equals 100 divided by ORR.)

AVI: Air Velocity Index: % Pred. MBC/% Pred. VC.

IIM: Index of Intrapulmonary Mixing: % conc. of Nitrogen in alveolar air after 7 minutes 100% oxygen breathing.

Blood Gases:

C_aO_2: *Arterial O_2 Content:* i.e., concentration of oxygen in arterial blood.

C_aCO_2: *Arterial CO_2 Content:* i.e., concentration of carbon dioxide in arterial blood.

S_aO_2: *Arterial O_2 Saturation:* $\frac{C_aO_2 \times 100}{\text{Art. } O_2 \text{ Cap.}}$

Arterial O_2 Capacity is the maximum amount of oxygen which can combine with a sample of arterial blood.

P_aO_2: Partial pressure of O_2 in arterial blood.

P_aCO_2: Partial pressure of CO_2 in arterial blood.

Plasma CO_2 C.P.: Plasma carbon dioxide combining power.

Art. pH.: Arterial hydrogen ion concentration in pH units.

Respiratory Gases:

I: Inspired Gas: The gas mixture inspired.

E: Expired Gas: The gas mixture expired.

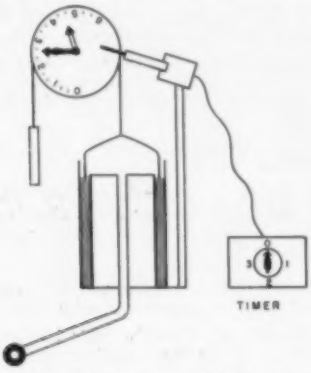
V_IO_2: Volume of O_2 inspired.

V_ECO_2: Volume of CO_2 expired.

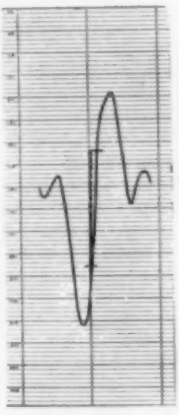
C_AO_2: Concentration of O_2 in alveolar gas.

P_ICO_2: Partial pressure of CO_2 in inspired gas.

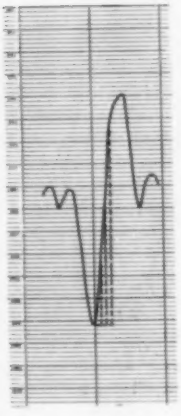
TIMED VITAL CAPACITY



VITALOMETER FOR TIMED V.C.



TIMED V.C.'S MEASURED WITH A RECORDING SPIROMETER



MID-HALF V.C. TIME

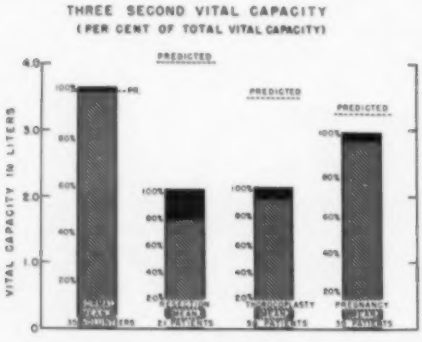
Timing of the Vital Capacity

Measuring the speed of performance of VC is as important as the measure of the volume of the total VC. It is one of the simplest methods for differentiating obstructive and restrictive ventilatory insufficiency. There are many methods for introducing the element of time into the vital capacity measurement.

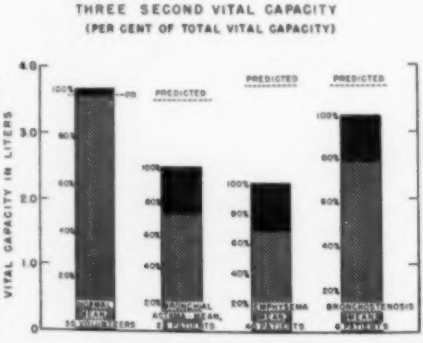
"Timed Vitalometer": An electronic timer (with selection for the desired time interval) actuates a solenoid which stops the recording of the VC at a pre-determined time interval.

Timed VC Measured with a Recording Spirometer: The desired time intervals are measured on the record of the vital capacity effort.

Mid-Half VC Time: Whereas the other two methods measure the volume of the VC exhaled in a given time, the mid-half VC time measures the time required for exhaling the middle half of the vital capacity. Normally this time interval is less than 4 seconds.



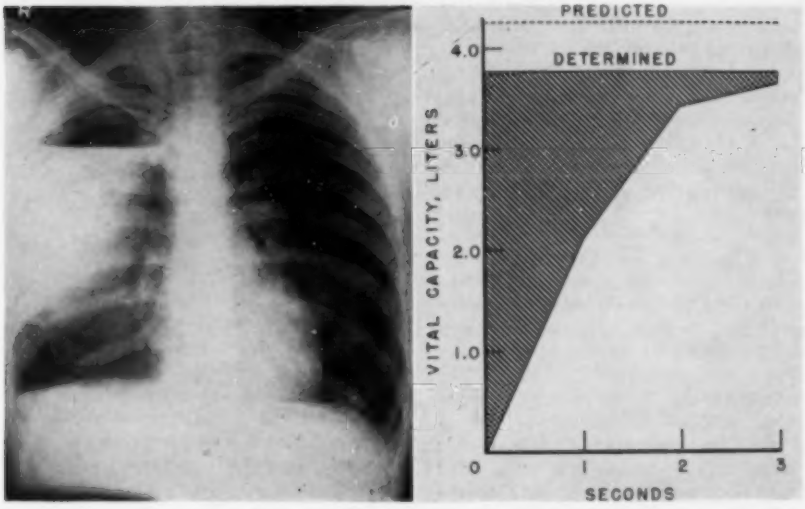
Restrictive ventilatory insufficiency.



Obstructive ventilatory insufficiency.

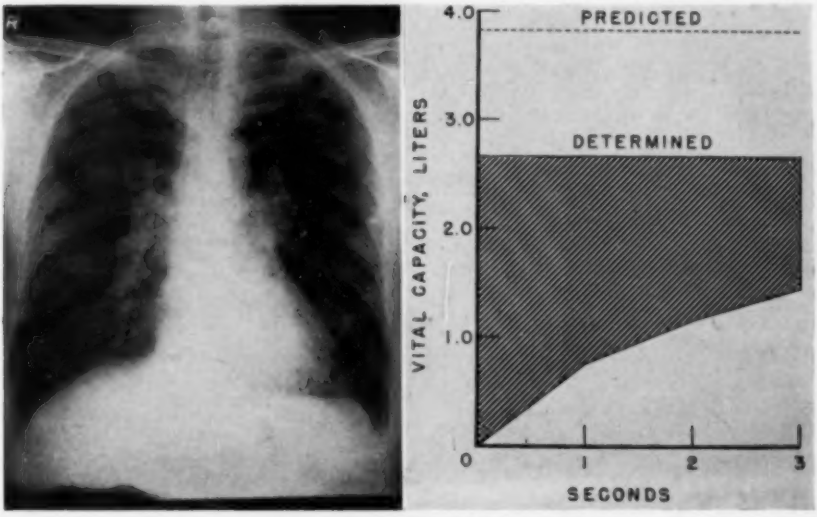
(from Gaensler, E. A., *Am. Rev. Tubere.*, 64:257-278, 1951.)

Restrictive Ventilatory Insufficiency



J. C. D.—36 year old male, oleo-pneumothorax: VC=3.776 L. (89% of predicted); 1 Sec. VC=2.108 L. (56% of total VC); 2 Sec. VC=3.425 L. (91% of total VC); 3 Sec. VC=3.645 L. (96% of total VC); MBC=155 L./Min. (117% of predicted).

Obstructive Ventilatory Insufficiency



H. L.—56 year old male, pulmonary emphysema, cor pulmonale: VC=2.664 L. (70% of predicted); 1 Sec. VC=0.755 L. (28% of total VC); 2 Sec. VC=1.155 L. (43 % of total VC); 3 Sec. VC=1.421 L. (53% of total VC); MBC=29 L./Min. (31% of predicted).

CLOSED CIRCUIT RESPIROMETRY

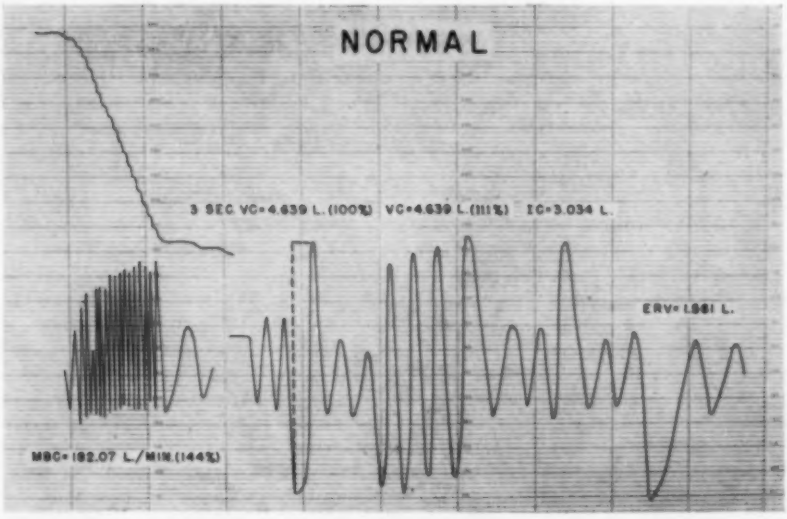
Spirograms are recorded data with the advantage that the qualitative aspects of breathing can be studied in addition to the measure of volume. They are useful for comparative purposes in which changes can be more completely evaluated. Spirograms in normals from day to day and week to week are uniform for the individual although they do vary from person to person.

There are two commonly used spirometers for closed circuit respirometer. They differ in size (9L and 13.5L). The larger spirometer offers the advantage of larger tubing and therefore lower resistance. Recording spirometers are usually equipped with two writing pens. The "spirograph" pen is a "direct" writing pen that records both inspiration and expiration. The "ventilograph" pen records the expiratory volumes only in a fixed ratio (1.10 for the 13.5L model) to the spirograph pen. This greatly facilitates measurement of ventilation volumes. The Kymograph runs at two speeds: 0.5 mm./sec. and 2.5 mm./sec.

Vital Capacity: Recorded at 2.5 mm./sec. for accuracy of measurement. The form of the inspiratory and expiratory curves can be seen readily. Total VC time and timed VCs can be measured. *Two Stage Vital Capacity:* obtained by adding the separate values for IC and ERV. *Air Trapping:* best demonstrated by successive determinations of the VC. If the VC becomes progressively smaller, trapping is present.

Maximum Breathing Capacity: Recorded at 2.5 mm./sec. The ventilation volume is measured from the "ventilograph" tracing. The normal MBC is performed below and above the baseline for tidal volume.

The accompanying spirograms were recorded on a Collins 13.5L. Spirometer.



Closed Circuit Respirometry

I. Kymograph run at two speeds: ½ mm./sec.; 2½ mm./sec.

II. The ventilograph pen records the total of Expiratory Volumes in a fixed ratio (1:10) to the spirograph pen.

III. Spirograms are recorded data that can be compared with future spirograms and progress and changes more easily evaluated.

IV. Spirograms in normals from day to day and week to week are uniform for the individual though they vary from person to person.

Breathing Patterns

I. With CO_2 absorber in place, O_2 consumption can be measured from the slope of the base line.

II. Ventilation is recorded by the ventilograph.

III. Tracings may help in evaluating the patient's cooperative effort and his general breathing patterns:
a) Hyperventilation
b) Irregular breathing patterns

IV. Paper speed ½ mm./sec. for O_2 consumption. Paper speed 2½ mm./sec. to study patterns.

Vital Capacity

I. Run at 2½ mm./sec. for accuracy of measurement.

II. An Expiratory VC followed by an Inspiratory VC. The two should be equal.

III. Not only total volume but total VC time and 1 sec. and 3 sec. VC can be measured and the form readily seen. Diminished 1 sec. VC is an indication of obstruction and/or loss of elasticity. The 3 sec. VC is the maximum useable volume of Vital Capacity.

IV. In obstruction—all patients should improve after adrenalin. (Increasing total volume with improved 1 and 3 sec. VC and shortened total VC time.)

Trapping

Air trapping is best demonstrated by three successive determinations of VC. VC becomes increasingly smaller where trapping is prominent. If this is due to obstruction which can be relieved, adrenalin will change the pattern toward normal.

Inspiratory Capacity and Expiratory Reserve Volume

I. Inspiratory Capacity and Expiratory Reserve Volume show changes in obstruction of acute nature, emphysema, fibrosis, and many other states including extrapulmonary lesions such as of cervical cord, etc.

II. Two state VC obtained by adding separate values for IC and ERV is equal to the one stage VC in the normal, but larger than the one stage VC in emphysema by a significant amount, and slightly larger in obstruction.

III. If Inspiratory Capacity is low and Expiratory Reserve Volume large due to obstruction that can be relieved, adrenalin should increase Inspiratory Capacity and reduce Expiratory Reserve Volume.

Maximum Breathing Capacity

I. Volume per minute can be measured from the ventilograph tracing.

II. Rate can be measured by counting.

III. Normal MBC is performed above and below the base line of the resting breathing pattern.

IV. Obstruction and loss of elasticity cause the MBC to be performed at high level to overcome obstruction and use what elasticity is still available.

V. If obstruction is temporary as in asthma, adrenalin will relieve it, increasing the MBC and lowering the level at which it is performed.

Restrictive Ventilatory Insufficiency

Spirographic Studies Characteristically Reveal:

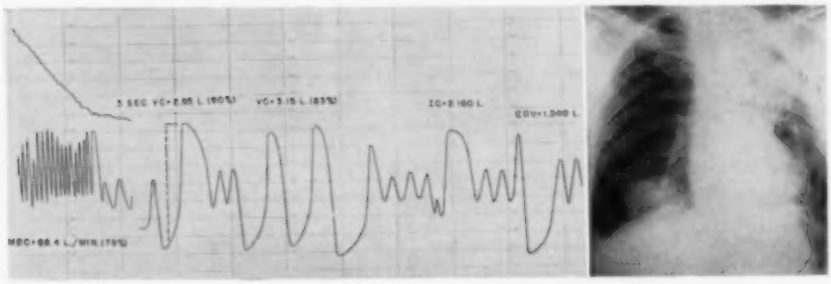
Loss of total lung volume with decreased vital capacity.

Absence of significant slowing in expiratory VC.

3 sec. VC=90-100% of total VC.

MBC normal or decreased, if reduced the reduction is disproportionately less than the decrease in VC.

MBC baseline level is not elevated.

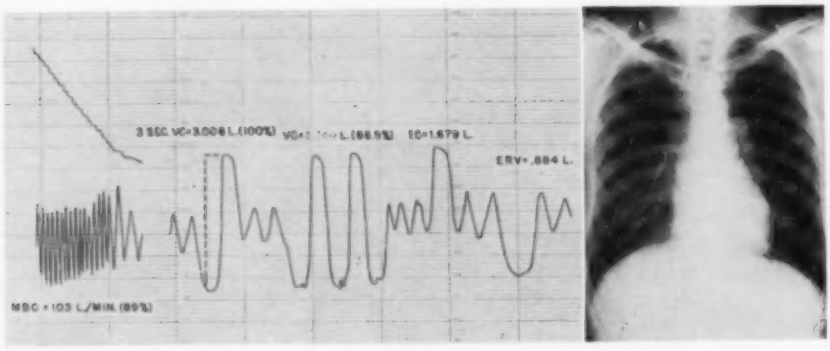


BRONCHOGENIC CARCINOMA

C. C.—58 year old male.

Chief Complaint—Cough, weakness and 20 pound weight loss for 5 months.

Additional Pulmonary Function Data —
RV/TLC x 100: 8%.
S_aO_2: 94.7%.
C_aCO_2: 52.5 vol. %.

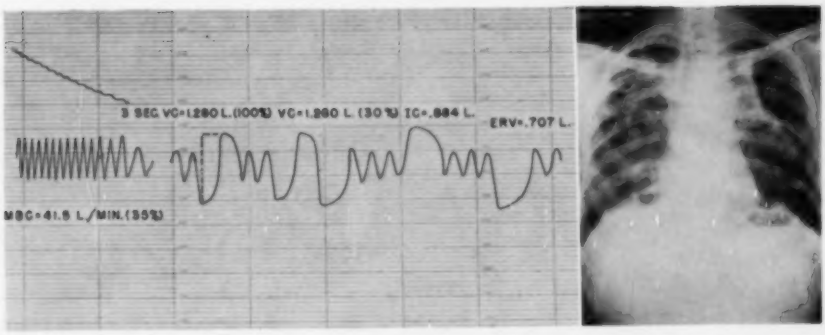


RHEUMATOID SPONDYLITIS
COCCIDIOMYCOSIS
(with cavitation in right upper lobe)

J. C.—24 year old male.

Chief Complaint—Mild chronic cough with hemoptyses for 6 months.

Additional Pulmonary Function Data —
RV/TLC x 100: 21%.



PULMONARY GRANULOMATOSIS (? Boeck's Sarcoid): *A. S.*—30 year old male.

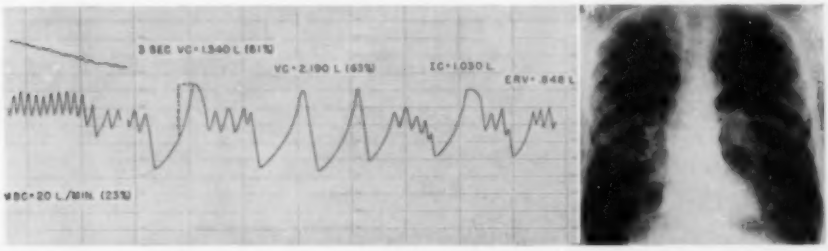
Chief Complaint — Dyspnea on exertion, weakness and 20 pound weight loss for 2 years.

Additional Pulmonary Function Data — RV/TLC x 100: 26%.

Obstructive Ventilatory Insufficiency

Spirographic Studies Characteristically Reveal:

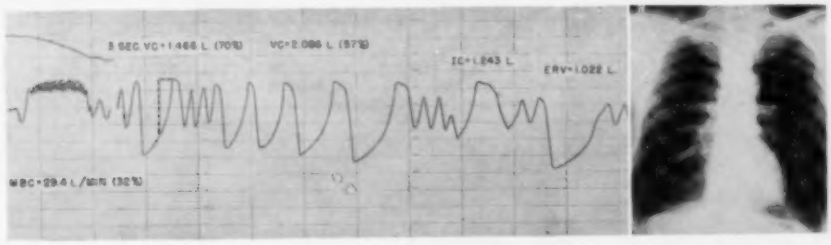
Total VC Normal or Decreased, Generally Decreased.
Prolongation of the Expiratory VC time. 3 sec. VC less than 90% of the total VC.
Two stage VC Greater than one stage VC.
MBC decreased and performed at an elevated baseline level.



PULMONARY EMPHYSEMA—PULMONARY FIBROSIS: *J. A.*—58 year old male.

Chief Complaint — Progressive exertional dyspnea and cough for nine years.

Additional Pulmonary Function Data — RV/TLC x 100: 48%.



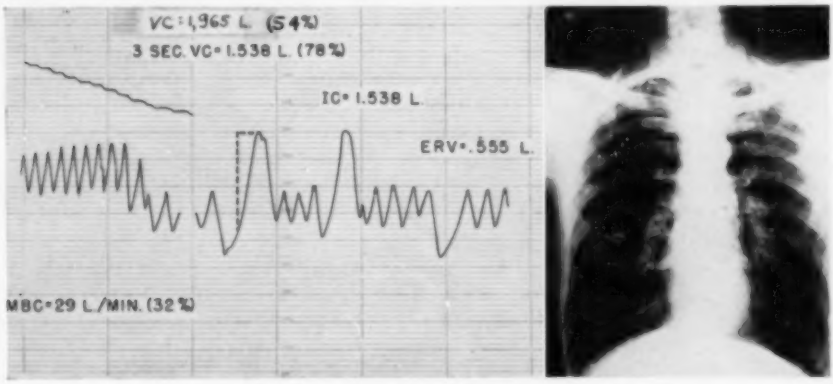
PULMONARY EMPHYSEMA—BRONCHITIS—CHRONIC: *C. B.* 59 year old male.

Chief Complaint — Chronic cough with mucopurulent sputum for four years. Progressive exertional dyspnea for one year.

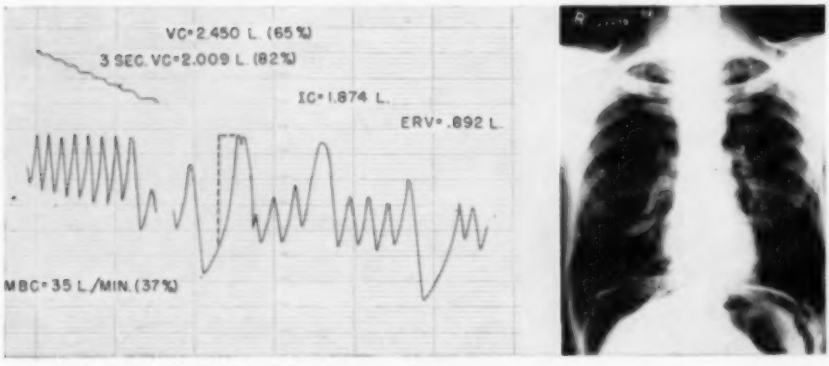
Additional Pulmonary Function Data — RV/TLC x 100: 89%.
S_aO_2: 89%.
C_aCO_2: 52.6 vol. %.

PULMONARY EMPHYSEMA—BRONCHIAL ASTHMA

R. R.—60 year old male: *Chief Complaint*—Asthma for twelve years. Progressive dyspnea on exertion for eight years.

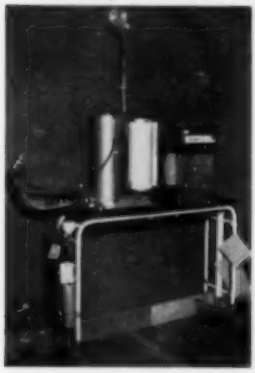


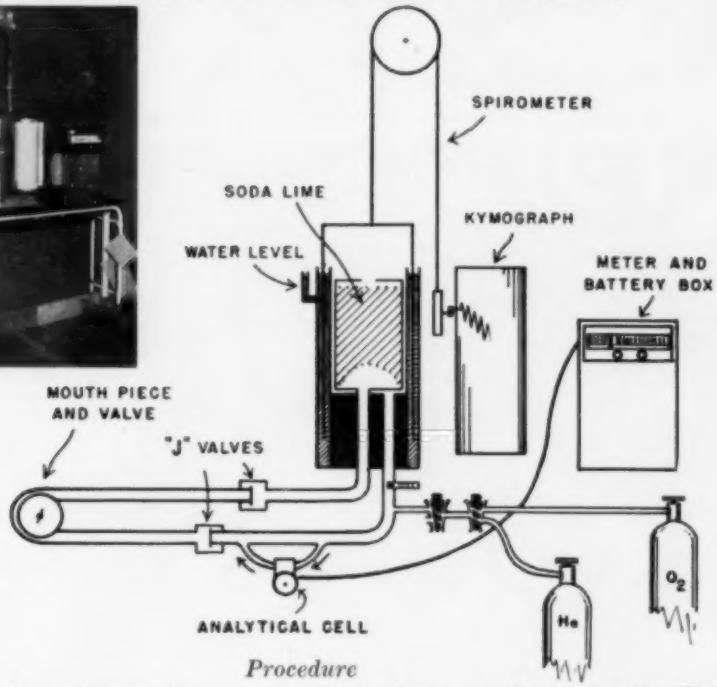
A. before therapy—*Additional pulmonary function data:*
RV/TLC x 100: 78%.



B. after bronchodilators, antibiotics and pneumoperitoneum—*Additional pulmonary function data:*
RV/TLC x 100: 61%.
S_aO_2: 94%.
C_aCO_2: 46 vol. %.

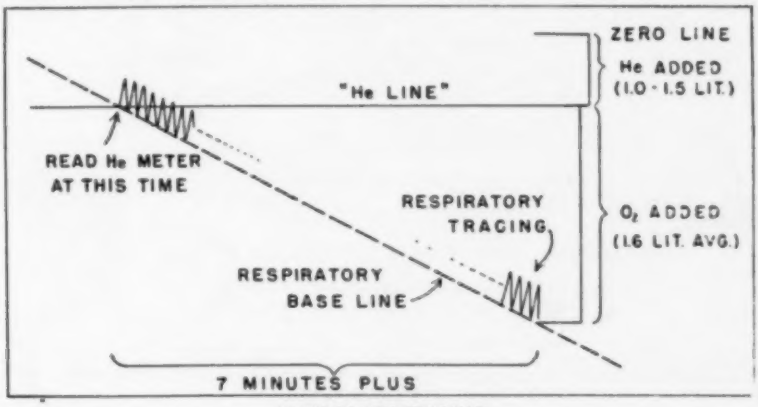
CLOSED CIRCUIT Functional Residual Capacity, Helium Method of Meneely and Kaltreider (*Proc. Soc. Exp. Biol. and Med.* 46:266, 1941.)





Procedure

1. Rinse spiro with room air.
2. Bring bell to "zero" volume and close valve.
3. Admit 1.0-1.5 liters helium and inscribe "He. Line."
4. Add enough O_2 for 7-10 minutes breathing.
5. Start kymograph and then connect subject.
6. Read helium meter at the time the respiratory baseline crosses the "He. Line."
7. Record bell temperature for correction of volumes to BTPS.
8. Inspiratory capacity and expiratory reserve volume are then measured for the lung volume calculations on the same spirometer with subject in same position as for FRC, usually semi-recumbent.

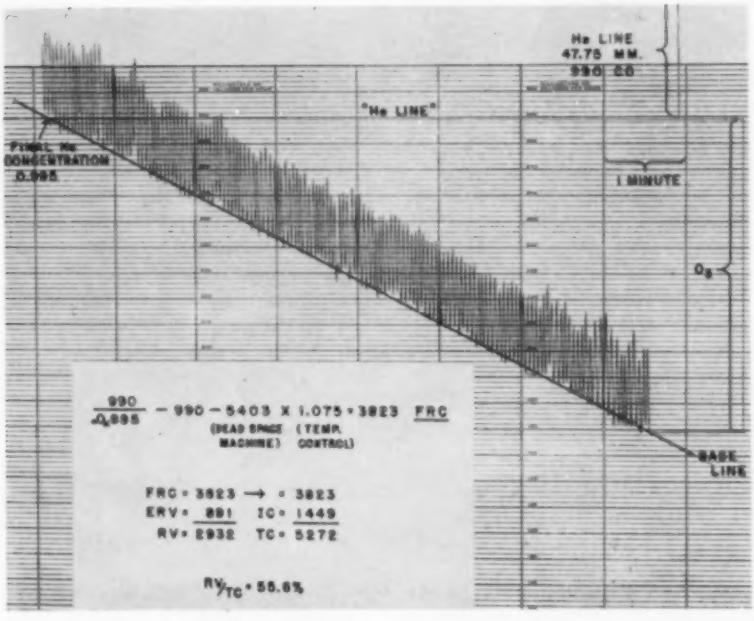


KYMOGRAPH TRACING

Calculations

$$\text{Dead space} = \frac{\text{He. added}}{\text{Final He. Conc.}} - \text{He. added}$$

$$\text{FRC}^* = \frac{\text{He. added}}{\text{Final He. Conc.}} - \text{He. added} - \text{Dead space}$$



Reproducibility of the Functional Residual Capacity:

(based on difference between first and second of 42 serial duplicate estimations with P = 0.05)

For all values of FRC (n = 42, o = 121 ml.):

Difference should not exceed	245 ml.
"Error" of Mean	±86 ml.

For FRC less than 5 liters (n = 29, o = 75 ml.):

Difference should not exceed	153 ml.
"Error" of Mean	±54 ml.

For FRC more than 5 liters (n = 13, o = 176 ml.):

Difference should not exceed	385 ml.
"Error" of Mean	±136 ml.

*This volume must be corrected to the observed baseline in the respiratory tracing, otherwise errors up to 600 ml. or more may result.

OPEN CIRCUIT

*Functional Residual Capacity, Oxygen Dilution Method of Darling, Cournand and Richards**

Modified from: Chronic Pulmonary Emphysema.
Physiopathology and Treatment (1953) by
M. S. Segal, M.D. and M. J. Dulfano, M.D.
with permission of the publisher, Grune and Stratton, Inc., New York City

Procedure

1. Rinse Douglas bag completely with "100% " O_2 and empty.
2. With valves A and B turned to outside air, connect patient with mouthpiece. (Fig. 1)
3. Allow tidal volume to become constant.
4. At the beginning of an inspiration turn valves A and B so that patient inspires "100%" O_2 and expires into the Douglas bag. (Fig. 2)
5. Seven and one-half minutes later, at the beginning of an expiration, return valves to original position. At the end of the expiration collect the "terminal" expiratory air sample at point C.
6. Mix gas in Douglas bag thoroughly. Collect a sample of gas from the bag and measure the total volume of the bag.
7. Analyze the "terminal" expired air sample and the Douglas bag sample for O_2 and CO_2 content.

A refinement of the open circuit method of measuring the FRC is the incorporation of a monitoring spirometer with "bag in box" to monitor the point in the vital capacity at which the patient is turned into the circuit for inspiration of oxygen and expiration into the Douglas bag. In this way, any error in starting the test at the beginning of an inspiration can be corrected. The monitoring spirometer is pictured in the illustration of an actual test.

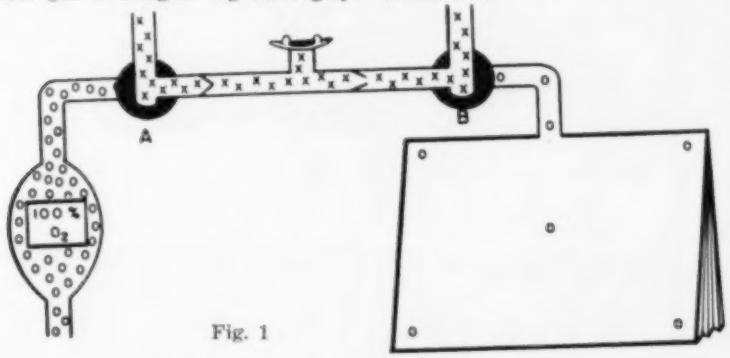


Fig. 1

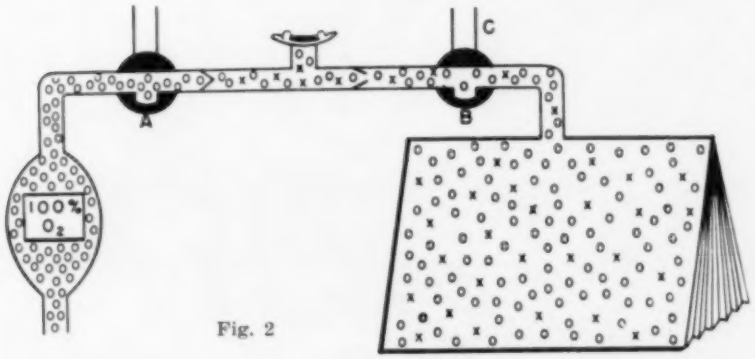


Fig. 2

20 % X
80 % O

*J.C.I. 19:609, 1940.

Calculations

$$\text{FRC (dry)} = \frac{(V)\ (b-a)-C}{\text{Alv. } N_s - \text{Alv. } N_p}$$

where FRC (dry) = functional residual capacity (cc.).

V = volume (cc.) in Douglas bag after 7½ min. oxygen.

b = per cent nitrogen in Douglas bag after 7½ min. oxygen.

a = per cent nitrogen in oxygen tank.

Alv. N_s = per cent nitrogen in alveolar air at beginning of procedure (average, 81.00%).

Alv. N_p = per cent nitrogen in alveolar air at end of 7½ min. oxygen (normal, 2.50%).

C = correction (cc.) for nitrogen excreted from body during 7½ min. oxygen: C = (B. S. m^2) (96.5) + 35.

DS = dead space (70 cc.).

$$\text{Example: FRC (dry)} = \frac{(8090)\ (.0537-.00352)-181}{.8109-.1026} = \frac{4073}{.708} = 5710 \text{ cc.}$$

FRC (dry) — DS x 1.066 = FRC (wet)

FRC (wet) — Exp. Res. Vol. = RV

RV — VC = TLC

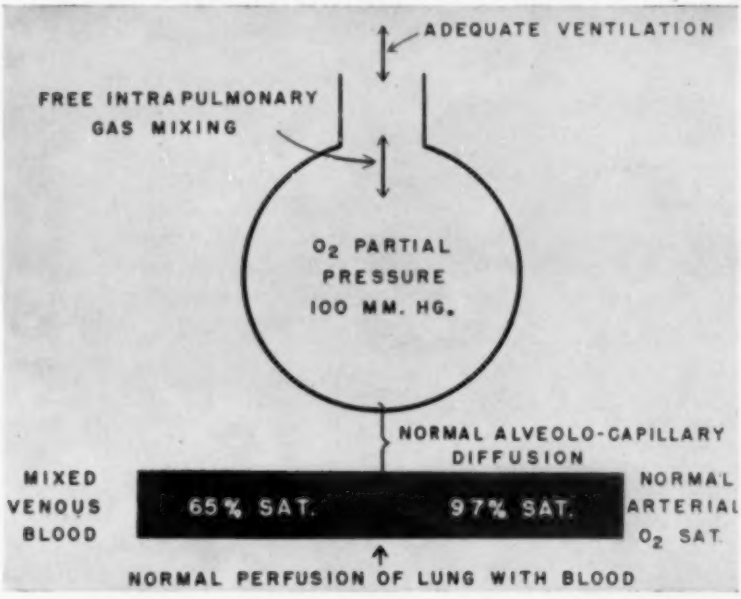
$$\text{Ratio} = \frac{\text{RV}}{\text{TLC}} \times 100$$

	Normal Patient	Emphysema Patient
Index IP mixing (Alv. N_p)	1.03%	10.26%
FRC (wet) cc.	3976	6012
Exp. Res. Vol. cc.	2150	1595
RV cc.	1826	4417
VC cc.	5609	3199
TLC cc.	7435	7583
Pred. TCC cc.	6719	5328
$\frac{\text{RV}}{\text{TLC}}$	25%	58%

ARTERIAL OXYGEN SATURATION IN PULMONARY DISEASE

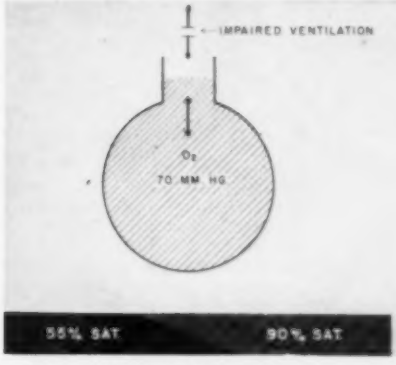
Anoxemia is reduced arterial oxygen saturation. In pulmonary disease, anoxemia may result from impaired ventilation, intrapulmonary gas mixing, diffusion or perfusion occurring singly or, more commonly, in combination.

Normal



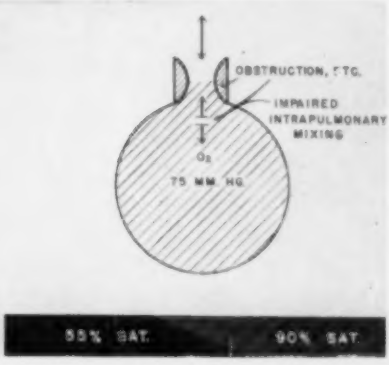
1. Lack of airway obstruction.
2. Good pulmonary elasticity
3. Normal size of alveolus.
4. Thin alveolar membrane
5. Normal alveolar capillary blood supply.

Impaired Ventilation



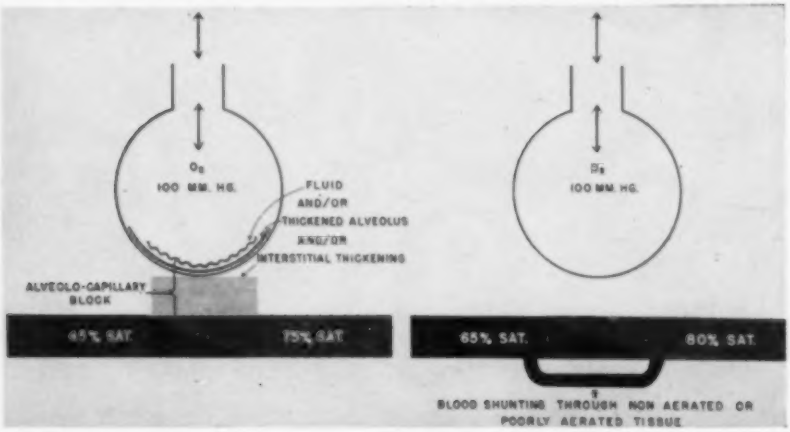
1. Depressed respiratory center.
2. Impaired thoracic cage mechanics.
3. Impaired diaphragmatic function.
4. Other causes of restriction of mobility of the lung.
5. Obstruction of respiratory passages.
6. Impaired pulmonary elasticity.
7. Pulmonary distention.

Impaired Mixing



1. The factors listed under impaired ventilation also apply to impaired intrapulmonary gas mixing.
2. Emphysematous bleb formation.
3. Air cysts.
4. Bronchiolar obstruction.
5. In chronic pulmonary disease these factors are generally progressive.

Impaired Diffusion *Impaired Perfusion (Shunting)*



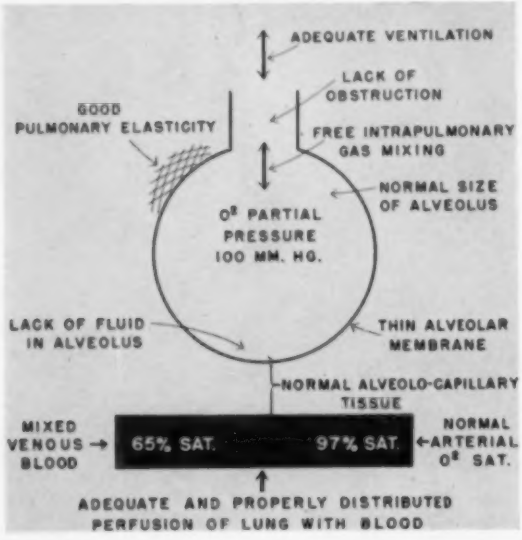
1. Fluid in alveolus.
2. Interstitial edema, fibrosis and inflammation.
3. Thickened pulmonary capillary.

1. Distribution of blood to non-aerated or poorly aerated lung tissue.
2. Pulmonary arteriovenous fistula.
3. Reduced pulmonary capillary bed.

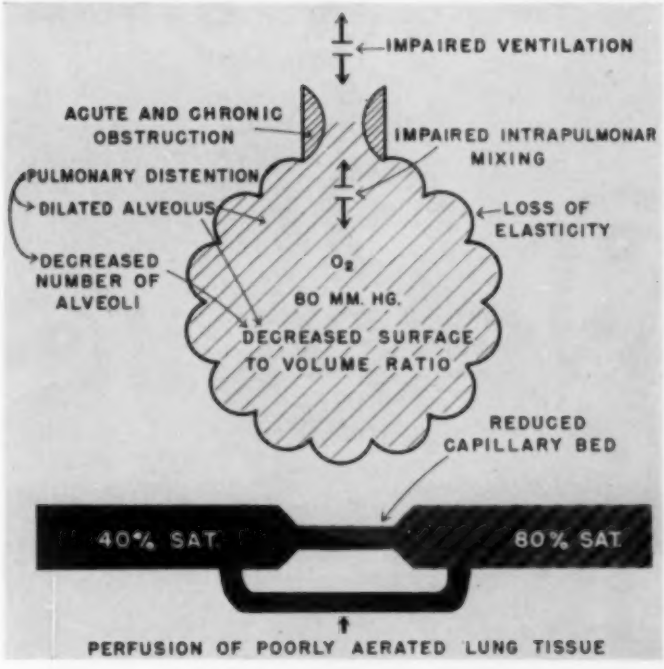
Congenital heart disease with a "right to left shunt" of blood may produce changes essentially identical to those seen with perfusion of non-aerated pulmonary tissue.

Normal

Determination of the arterial oxygen saturation is useful in the evaluation of patients with pulmonary disease. The primary factors which govern the arterial oxygen saturation and likewise, the factors which may be evaluated by a determination of the arterial oxygen saturation are: ventilation, intrapulmonary gas mixing, diffusion, and perfusion. Measurement of the arterial oxygen saturation is useful as an overall test of the four factors listed above but will not delineate specific impairment of these functions. Combined with other studies it is helpful in the separate evaluation of the four factors. More elaborate blood gas studies are necessary for specific delineation, especially of diffusion and perfusion. Although the arterial oxygen saturation is useful in assessing the ability of the lung to oxygenate blood, it is not the most sensitive measure of this function. More elaborate blood gas studies may reveal impaired diffusion in some patients who have normal arterial oxygen saturation.

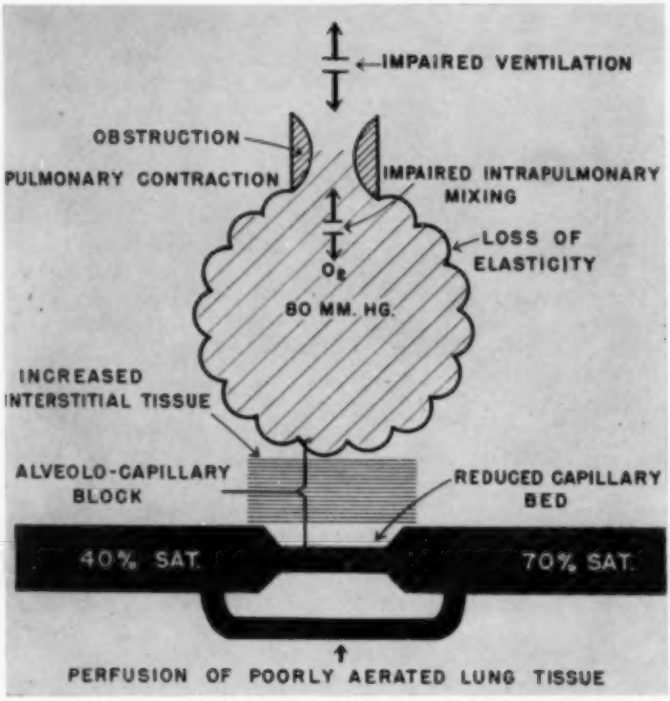


Pulmonary Emphysema



In the usual case of pulmonary emphysema with arterial oxygen unsaturation no single function is wholly responsible for the impairment of oxygenation. Usually, ventilation, intrapulmonary gas mixing, diffusion, and perfusion are all impaired and it is not possible to quantitate impairment of any one function. Determination of the arterial oxygen saturation in pulmonary emphysema is frequently used in combination with the measurement of arterial carbon dioxide content for classification of the severity of the disease. This is especially true when the measurements are made during exercise as well as at rest. In addition, serial determinations of arterial oxygen saturation in any given patient with pulmonary emphysema are helpful in determining the type of therapy and evaluating its effectiveness.

Pulmonary Fibrosis

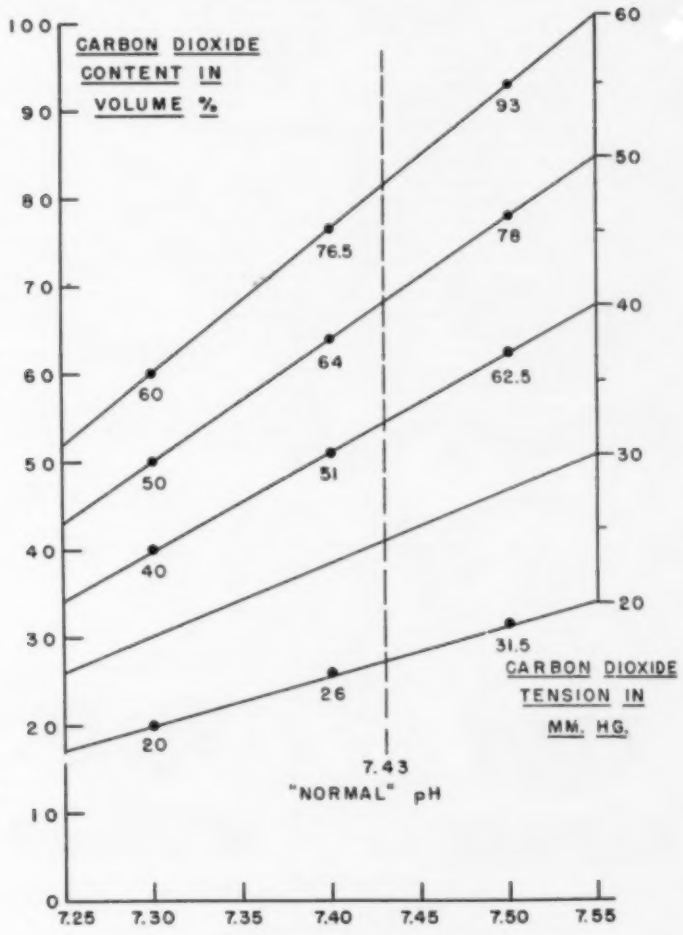


In pulmonary fibrosis, there may be much variation in impairment of pulmonary function. Thus, the arterial oxygen saturation in patients with different types of pulmonary fibrosis is highly variable. In these cases of pulmonary fibrosis which lead to airway obstruction, pulmonary emphysema is frequently found.

The arterial oxygen saturation will be influenced not only by the basic lesion but also by the factors discussed under pulmonary emphysema. In some patients with pulmonary fibrosis, diffusion of gases across the alveolocapillary membrane is the only significant lesion. (The alveolocapillary block syndrome.) Measurement of the arterial oxygen saturation may be most helpful here for it may be the only commonly determined measurement which is significantly impaired.

In addition to the specific classes of pulmonary fibrosis discussed above, there are cases of pulmonary fibrosis with no impairment of oxygenation of the blood. Thus, a normal arterial oxygen saturation may be helpful.

ARTERIAL CARBON DIOXIDE AND pH



RELATION OF CARBON DIOXIDE TENSION, CARBON DIOXIDE CONTENT AND pH

Controlled carbon dioxide elimination is as important a function of respiration as oxygenation. When carbon dioxide is released from body cells into the blood it forms H_2CO_3, an acid. This acid combines to some extent with the base of blood. Depending upon the amount of base and upon the amount of carbon dioxide, there will be more or less "free" dissolved carbon dioxide. *Carbon dioxide tension* (partial pressure of CO_2) is the measure of "free" carbon dioxide. *pH*, the measure of relative acidity or alkalinity of the blood, is dependent upon the amount of base and the amount of carbon dioxide in the blood at the moment.

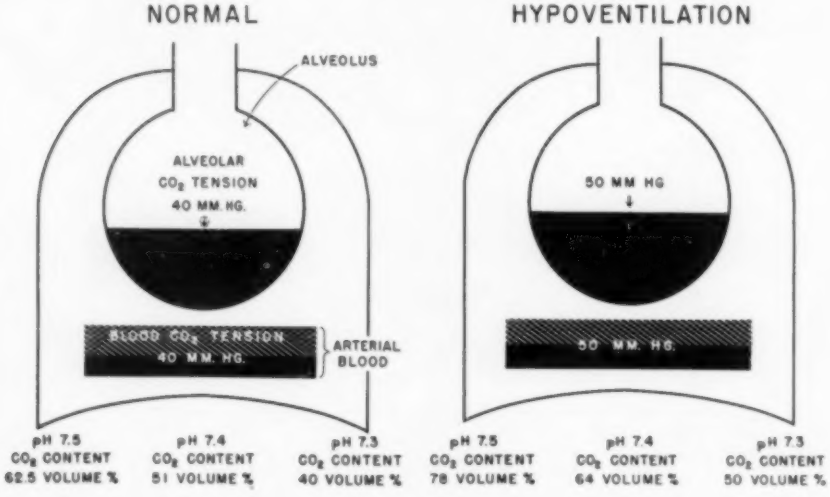
Since carbon dioxide is highly diffusible, the carbon dioxide tension of arterialized blood leaving an alveolar capillary network is almost exactly the same as the carbon dioxide tension of the gas in that alveolus. This remains true even when alveolocapillary oxygen diffusion is severely impaired because carbon dioxide is so much more highly diffusible than oxygen. Alveolar carbon dioxide tension therefore "controls"

arterial carbon dioxide tension, even in advanced pulmonary impairment. Alveolar carbon dioxide tension in turn depends upon the quantity and quality of ventilation and intrapulmonary gas mixing.

The amount of base in the blood is controlled principally by the kidney. It normally retains extra base (principally sodium) when pH shifts toward the acid side. This compensatory renal process is slow (days) compared to the pulmonary regulation of alveolar CO_2 (seconds). The pH of the blood is directly dependent upon the relative amounts of CO_2 and base present. The retention or excretion of base by the kidney may be regarded as the "fundamental" factor in acid-base balance, but pulmonary regulation of alveolar and so of arterial CO_2 tension is the "immediate" factor since normally it can alter alveolar CO_2 and so arterial CO_2 almost instantaneously. From moment to moment, then, pulmonary regulation of CO_2 tension is the major factor in maintaining blood pH. Serious consequences rapidly result if blood pH is not held virtually constant at 7.43. Therefore it is not enough for the lungs merely to eliminate CO_2 from the body, they must do it in such a manner that blood pH is controlled within narrow limits.

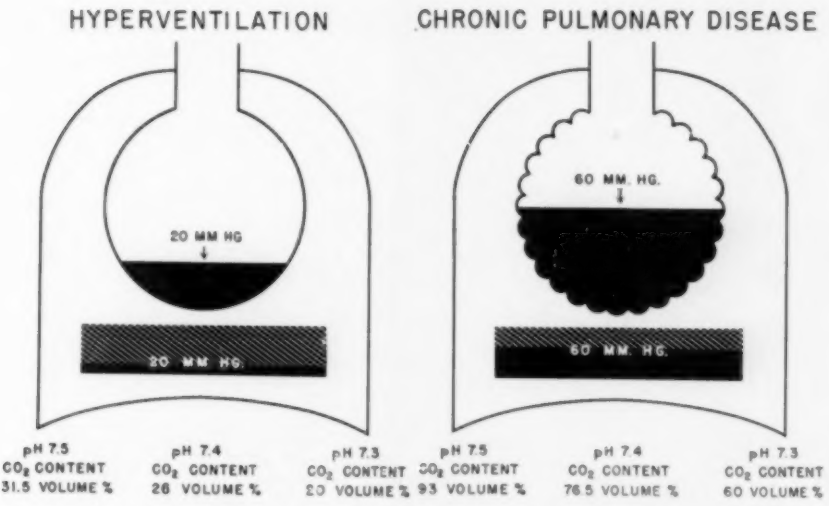
There are many methods to measure arterial CO_2 tension and arterial pH. For the pulmonary physiologist the easiest adequate method depends upon certain relations which have been found to exist between pH, CO_2 content and CO_2 tension. The CO_2 content of an arterial blood sample can be measured with the Van Slyke manometric apparatus and its pH measure directly with a glass electrode pH meter. With this information arterial CO_2 tension can be read from a graph.

In pulmonary function testing, arterial pH determination is of importance largely because when it is known and when arterial CO_2 content is known, arterial CO_2 tension may be derived. This latter is closely related to alveolar CO_2 tension which in turn is an excellent measure of the adequacy of ventilation and intrapulmonary gas mixing.



With normal ventilation and intrapulmonary gas mixing, the partial pressure of CO_2 in the alveoli is usually 40 mm. Hg. Normally there is no significant alveolar-arterial blood CO_2 gradient. Thus, for blood leaving any given pulmonary capillary the partial pressure of carbon dioxide in that capillary will be the same as the partial pressure of CO_2 in that alveolus. With normal alveoli and pulmonary capillaries throughout the lung, the partial pressure of carbon dioxide in arterial blood is 40 mm. Hg. With a normal blood base, the pH will be normal.

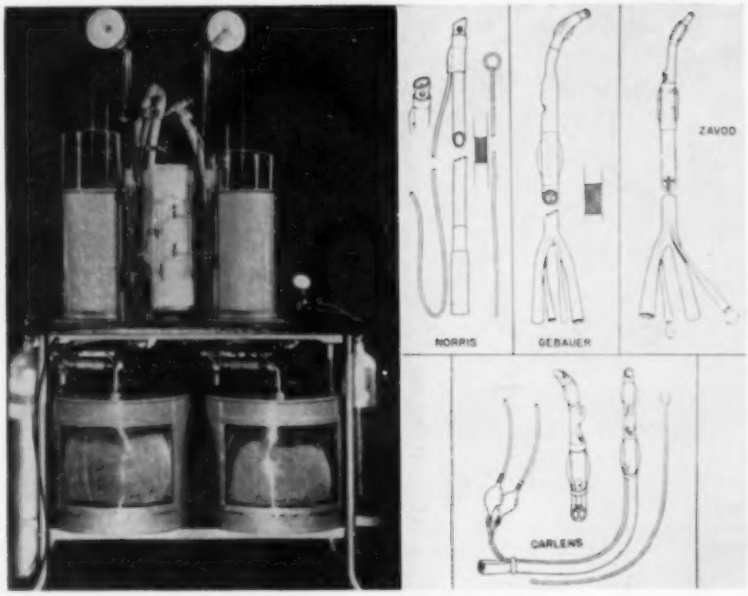
Inadequate ventilation for any reason results in an increase in the partial pressure of CO_2 in the alveolus. Since the arterial blood P_{CO_2} is in equilibrium with the alveolar P_{CO_2}, there will be an increase in arterial P_{CO_2}. Acutely this CO_2 retention causes lowering of the pH, and is known is respiratory acidosis. If CO_2 retention persists renal retention of base raises pH to normal compensating for the high CO_2 tension. This condition is then compensated respiratory acidosis.



Emotion, drugs, central nervous system disorders, high altitude and other factors may cause hyperventilation. With hyperventilation excessive CO_2 is "blown off" and the alveolar P_{CO_2} is lowered. Acutely, this results in a decreased arterial P_{CO_2} and increased pH. This situation is known as respiratory alkalosis. With prolonged hyperventilation renal loss of base raises the pH and leads to a compensated respiratory alkalosis. Prolonged hyperventilation rarely occurs as a result of pulmonary disease, but is of importance in understanding pulmonary function in certain situations (i.e., respirator patients).

In chronic pulmonary disease the usual abnormality of arterial CO_2 and pH is that which accompanies hypoventilation. Thus, there is usually a respiratory acidosis which may or may not be compensated. In addition by the time CO_2 retention and acidosis occur, anoxia will also be present. In these patients, anoxia is the main stimulus to ventilation because the respiratory center has become insensitive to CO_2. Oxygen therapy may abolish the anoxia and further depress respiration. Further retention of CO_2 may occur rapidly and lead to CO_2 narcosis and even death if steps are not taken to insure adequate ventilation.

BRONCHOSPIROMETRY

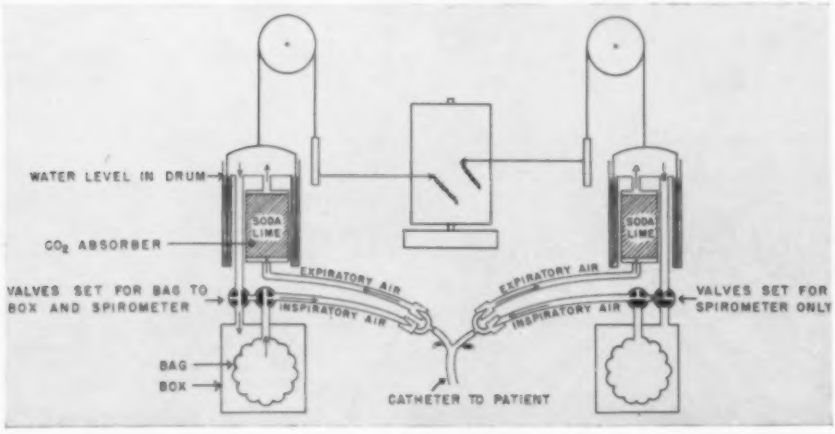


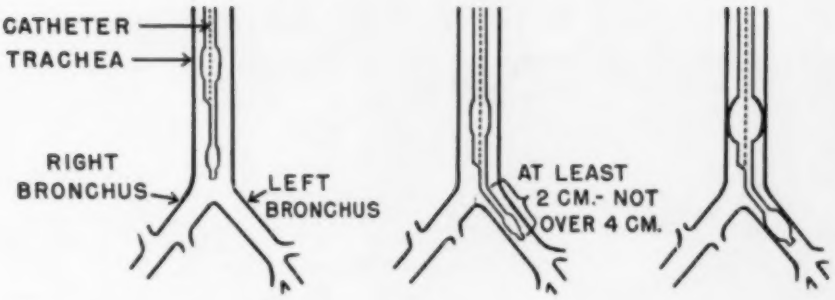
Indications:

For collapse therapy, surgery, following unilateral progressive disease, etc., where is it necessary to know how much each lung is contributing.

Contraindications:

1. Ulcerative tracheobronchitis.
2. Recent hemoptysis in tuberculosis (within two weeks).
3. Tracheobronchial deformities.
4. Strictures of the left main stem bronchus makes it necessary to put the catheter in the right main stem bronchus which alters results because resistance is greater on the left.
5. In bronchiectasis daily sputum must be well controlled before attempting procedure.
6. Dyspneic patients may have difficulty.
7. Uncontrolled cough and secretions.

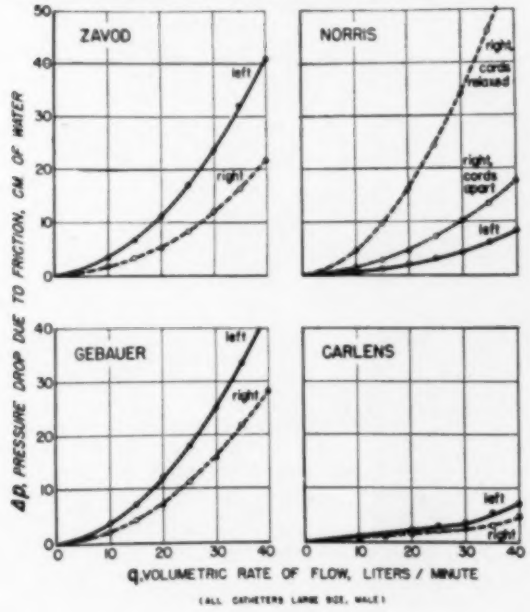




Procedures Done

1.	Differential O_2 uptakes	Routine
2.	Differential vital capacities	
3.	Differential resting ventilation	
4.	Differential Functional Residual capacity	Special
5.	Differential intrapulmonary mixing	
6.	Differential studies with exercise	

BRONCHOSPIROMETRIC CATHETER RESISTANCE

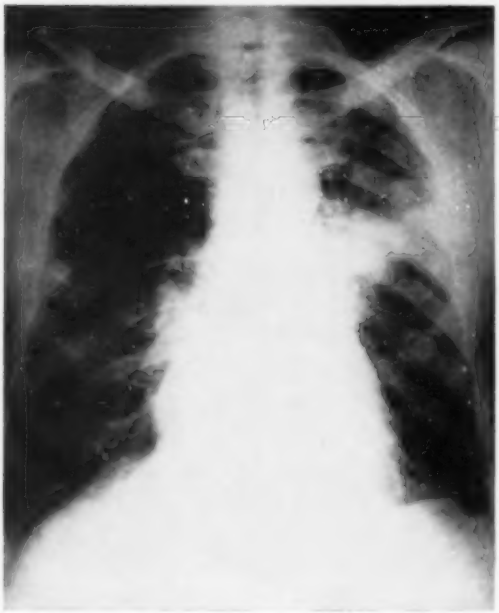


(ALL CATHETERS LARGE SIZE, MALE)

Precautions during bronchospirometry assuring reliable results:

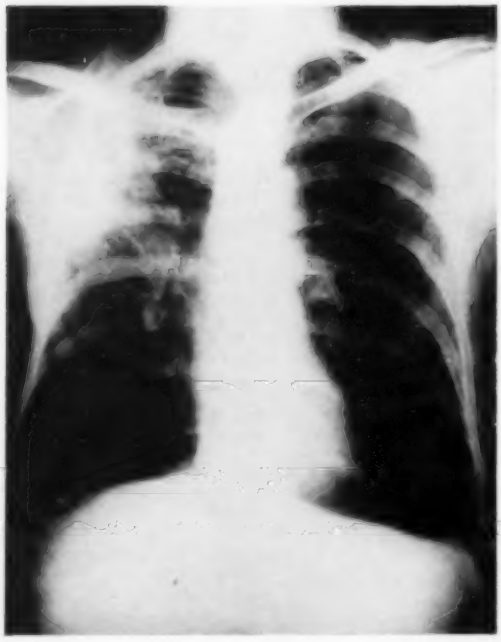
1. Adequate topical anesthesia to trachea and bronchi.
2. If cough or uncontrollable secretions occur, procedure should be abandoned and repeated another day.
3. Catheter should be placed at least 2 cm. and not over 4 cm. into the left main stem bronchus.
4. A tracing should be made with catheter in place and observations of position made before and after. This serves as a good control for later tracings, and to insure catheter being well placed.
5. Some catheters develop leaks from one main lumen to the other.

FLUOROSCOPIC ESTIMATE OF PULMONARY FUNCTION



Fluoroscopy is a supplement to volume measurements and allows one to see time factors. It does not tell how much air is breathed, but it makes visible:

1. The SPEED with which air can be drawn in and forced out.
2. The MECHANICS of breathing: *a*. Diaphragmatic; *b*. Abdominal; *c*. Intercostal; *d*. Accessory.
3. AERATION — relative lucency during inspiration and expiration in:
   a. Apex; *b*. Base.
4. Abnormal MOTILITY or FIXATION:
   a. Hila; *b*. Mediastinum; *c*. Other "mid-line" structures; *d*. Peripheral lung markings.
5. Differences between the lungs and segments of a lung with respect to the above.
6. Evidence of the nature of CYSTS:
   a. Freely communicating; *b*. Ball-valve; *c*. Closed.



The Diaphragm

Functionally there are two diaphragms, right and left.

1. Note POSITION and CONTOUR. *a*. Low? *b*. Flattened? *c*. Depressed? *d*. Tenting?
2. Note MOTION — degree and equality on quiet breathing, deep breathing and sniff.
   a. Are descent and ascent similar in duration, and equal right and left? *b*. Is direction of motion normal or paradoxical? *c*. Is quiet expiration normal and deep expiration prolonged — unilateral or bilateral? *d*. One portion of one leaf of diaphragm may be restricted, fixed, or paradoxical, and may give rise to a "hinge" type of motion. 1. Examine in A-P and oblique.
3. Does suprapubic fist pressure alter the excursion of the diaphragm?
4. Look for DELAYED AND PROLONGED ASCENT of one or both diaphragms (EXPIRATORY TRAPPING)
   a. On deep breathing? *b*. On rapid, forced breathing?

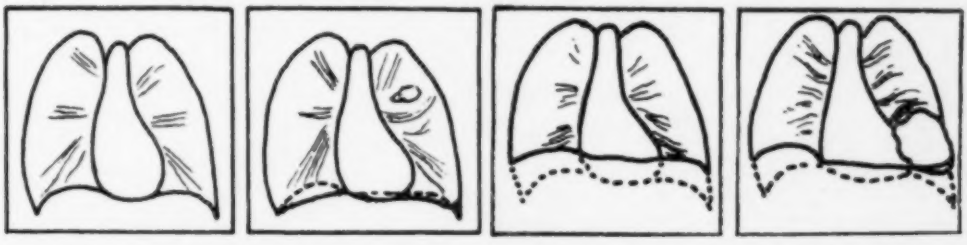
The Midline Structures

1. Open screen to full vertical aperture and narrow horizontally to OBSERVE DURING QUIET AND DEEP BREATHING:
   a. Heart
   b. Mediastinum
   c. Hila
   d. Trachea
2. ON DEEP INSPIRATION, heart, trachea and hila normally elongate and remain in midline position.
   a. Inferior hilar markings normally elongate more than superior ones.
3. ON FORCED EXPIRATION should see:
   a. Midline structures return to normal
   b. Freely compressible hilar marking
   c. Heart may normally rotate, according to habitus
4. SHIFT of midline structures is due to INEQUALITY OF INTRATHORACIC PRESSURES.
5. If structures shift to one side:
   a. Note DIRECTION and AMOUNT of shift, and PHASE OF BREATHING during which it occurs.
   e.g. "Mediastinum and heart shift to right @ 2 cm. with deep inspiration.")
   b. Note if structures return to midline or swing to opposite side during opposite phase of breathing.
   c. Note in SEQUENCE the following in relation to the shift to help explain its cause:
      1. Diaphragmatic motion
      2. Intercostal motion
      3. Relative width of each hemithorax
      4. Differences in lucency of right and left lower and upper lung fields
      5. Differences in motility or fixation of peripheral and midlung marking
      6. Evidence of rotational movement of perihilar markings.

The Hila

1. Observe RIGHT and LEFT hilus separately
2. Each hilus has SUPERIOR and INFERIOR DIVISION
   a. Greater motility of inferior division during deep breathing
3. REDUCED MOTION of hilar markings caused by:
   a. Restricted diaphragmatic motion
   b. Pulmonary fibrosis
   c. Inflammatory or neoplastic fixation
   d. Apical and subapical pleural symphysis (superior hilus)
4. COMPRESSION OF HILUM may be seen during expiration when expiratory trapping is marked (emphysema)
5. ROTATIONAL MOVEMENT of hilum due to:
   a. Relative fixation of hilus centrally, periphery free
   b. Segmental peripheral fixation of hilus, center free
   c. Marked differences in intrapulmonary pressures between adjacent segments (tension cyst, segmental atelectasis)

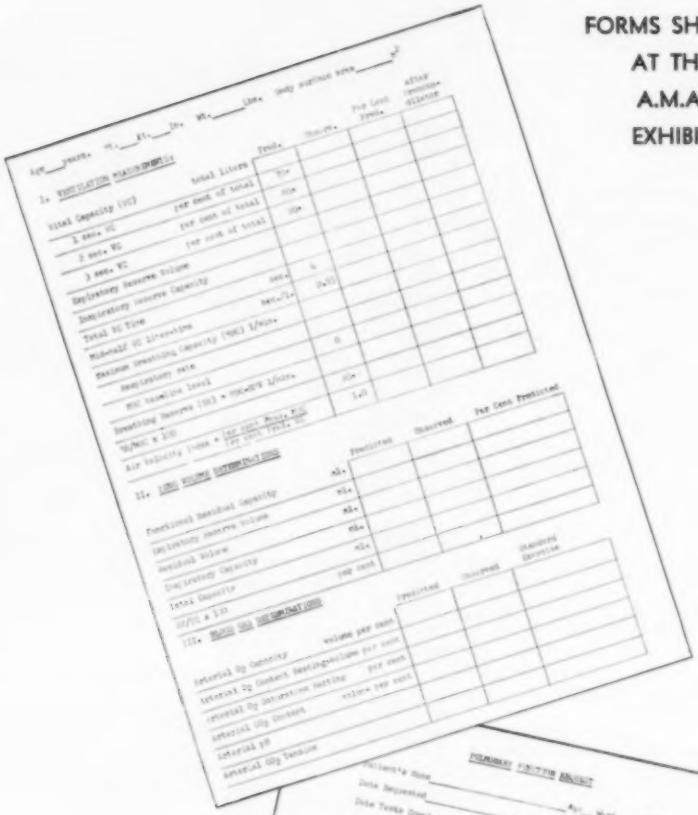
Intercostal Movement and Peripheral Lung Marking



Breathing may be largely intercostal in some people.

1. Note that intercostal motion is seen best during deep breathing.
   a. Examine in A-P and P-A.
2. Note that intercostal motion is normally less over upper lung field than lower.
3. Note any inequalities of costal movement, comparing right and left sides of the upper, middle and lower lung fields.
   a. Use narrow vertical screen aperture and full screen horizontally.
4. Local reduction of costal movement or reduced mobility of peripheral lung markings may be due to:
   a. Old or recent pleural involvement.
   b. Inflammatory or neoplastic disease.

FORMS SHOWN
AT THE
A.M.A.
EXHIBIT



PULMONARY FUNCTION ANALYSIS

Patient's Name
Date Requested
Date Tests Completed
Requisition made by Doctor
1. Diagnosis
2. Indication of degree of pulmonary disability (check one):
(a) None (b) Slight (c) Moderate (d) Severe
3. Dyspnea (check one):
(a) None (b) With moderate exercise (c) With mild exercise
(d) At rest
4. Please check any of the following disease processes suspected (one or more):
(a) Pulmonary emphysema (b) Bronchial asthma (c) Bronchiectasis
(d) Chronic bronchitis (e) Diffusion impairment (f) Fibrosis of pleura
(g) Constriction (h) Atelectasis (i) Diffuse Pulmonary Fibrosis
(j) Pleural disease (Thoracoplasty) (k) Other (specify)
5. Has the patient ever had tuberculosis (Yes) (No) (Unknown)
now (Yes) (No) Is disease inactive (Yes) (No)
6. Previous thoracic surgery
(a) Procedure Date
(b) Procedure Date
7. Contemplated thoracic (or other) surgery
(a) Procedure When contemplated
8. Medications (except those patient is receiving):
(a) Narcotic (b) Bronchodilatory, oral (Aminophyllin/Ephedrine)
(c) Expectorants
9. Please indicate the particular information about the patient which you desire from these tests
10. Previous pulmonary function studies (Yes) (No)

	Predicted	Observed	Per Cent Predicted
Functional Residual Capacity	ml.		
Inhalation Reserve Volume	ml.		
Residual Volume	ml.		
Vital Capacity	ml.		
Inhale Capacity	per cent		

	Predicted	Observed	Observed Corrected
Interval by Gasometry volume per cent			
Interval by Indirect Spirographics per cent			
Interval by Inhalation Testing per cent			
Interval by Oximeter volume per cent			
Interval pH			
Interval Alg Tension			

Special Exhibit on Pulmonary Function Testing

The Special Exhibit on Pulmonary Function Testing is presented by the Section on Diseases of the Chest of the American Medical Association. It has been developed and continued with the help of many individuals, under the auspices of the following General Committee and representatives of Government Services:

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Linde Air Products Co., Birmingham, Alabama
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The Picker X-Ray Corp. Fluoroscope was provided for the 1954 exhibit by Sicular X-Ray Corp., 1420 Sutter St., San Francisco, California
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PULMONARY FUNCTION TESTING

A Special Exhibit from the Section on Diseases of the Chest

Acknowledgments

These panels were prepared for a special exhibit from the Section on Diseases of the Chest of the American Medical Association with the cooperation of the Joint Committee on Occupational Diseases of the Chest of the American College of Chest Physicians, the Industrial Medical Association, and the American Trudeau Society; the Committee on Occupational Diseases of the Chest and the Committee on Physiologic Treatment, Council on Research, American College of Chest Physicians and the Veterans Administration Committee on the Cooperative Study of Pulmonary Function Testing.

Many individuals participated in the preparation of this exhibit. Particular thanks are due to Dr. Maurice Segal, Boston, who provided the material for the panel devoted to the open method for F.R.C. of Darling, Cournand and Richards (J.C.I. *19:* 609, 1940); to Dr. Julius Comroe, Jr., Philadelphia, for some of the material presented in Definition of Objectives and for other helpful suggestions; to Dr. Edwin Gaensler, Boston, for the material concerning Bronchospirometry; to Dr. John Seabury, New Orleans, for the material concerning Fluoroscopy and to all others who generously helped in many ways. The arrangements for the exhibit were made by Dr. Edwin R. Levine, Chicago, Representative of the Section on Diseases of the Chest to the Scientific Exhibition of the American Medical Association. The other officers of the Section on Diseases of the Chest have, by their individual and collective cooperation, contributed in a major way to this project. For the participation of The American College of Chest Physicians, of the officers of the College and of its Executive Administration, particularly for the tireless and effective assistance of Mr. Murray Kornfeld and his staff, the physicians concerned with this project give special thanks.

Those who have worked on this Exhibit feel a deep sense of gratitude to Dr. Thomas G. Hull, Secretary, Council on Scientific Assembly, American Medical Association, to Mrs. Hull and to Miss Frances Nyberg, Secretary to Dr. Hull, for all their help and guidance.

The material for the panels was assembled in the Radioisotope Service and Research Laboratory of Thayer Veterans Administration Hospital, Nashville, Tennessee, and prepared for presentation by Dr. Donald S. Tysinger, Jr., Dr. James J. Callaway, Dr. Joseph M. Merrill, and Mrs. Con O. T. Ball.

The Fluoroscopy posters were prepared in the Department of Medical Illustration of Louisiana State University, Mr. Gerald Hodge, Director. The other panels were prepared and the whole exhibit completed in the Medical Illustration Laboratory, Thayer Veterans Administration Hospital, Nashville, Tennessee, by Mr. Homer Jones, Chief, and Mrs. Ann Marshall Rees, Medical Artist.

George R. Meneely, M.D.
Chairman

A More Direct Liquefaction of Bronchial Secretion by Aerosol Therapy

EDWIN RAYNER LEVINE, M.D., F.C.C.P.*
Chicago, Illinois

In the management of bronchopulmonary disease, the problem of bronchial secretion is frequently the most difficult of solution. To maintain a free airway, it is necessary to eliminate this secretion with the least possible irritation. In many cases, the mucopurulent material in the bronchus is thick and tenacious and may be an obstruction or an irritant to the bronchial tree. Cough increases this irritation and must be long and vigorous before such viscous material can be eliminated. It is in this type of case that aerosol therapy has become a regular form of treatment. It is important, however, to remember that such therapy is only one approach to the liquefaction of viscous secretion and should be used in combination with other types of therapy to produce the best result.

Of primary importance in the management of bronchial secretion and bronchial irritation, is the question of humidity of the inspired air. All of the air that reaches the alveoli must be completely saturated with water vapor. The moistening of inspired air is a function of the nasal mucosa and the tracheo-bronchial tree. If the inspired air is too dry, if its relative humidity is too low, the amount of moisture that is absorbed from the mucosa of the tracheo-bronchial tree may be sufficient, in the case of bronchial infection, to remove liquid that would otherwise be part of bronchial secretion. This is, to put it simply, a mechanism of drying, and mucus in drying becomes more tenacious, more viscous and more difficult to eliminate. Consequently, in many cases, the maintenance of adequate humidity in the inspired air, either by humidifying the environmental air or by the inhalation of water vapor, is a most valuable method of preventing and relieving the formation of excessively viscous mucus.

Another point that should be remembered is that all of the liquid that appears in the bronchus must come from the blood stream. If the liquid intake is insufficient, and if the patient shows any degree of dehydration, no matter how slight, there is likely to be an insufficient amount of moisture and the same result of drying will be accomplished. When hyperpnea occurs, the volume of air requiring moisture is increased. If the air is dry or the liquid intake inadequate, hyperpnea increases the drying effect in the bronchial tree.

When bronchial secretion is thick, potassium iodide, ammonium chloride and similar preparations are capable of liquefying this secretion. Where it is possible for the patient to use drugs of this group, it may be an effective method of ensuring a sufficiently liquid secretion to accomplish all the

*From the Medical Department of The Chicago Medical School and Edgewater Hospital.
Aided, in part, by a grant from the Research Foundation for Diseases of the Chest.

ends of proper elimination. But there is a large group of cases where the methods mentioned above are inadequate because of the chronicity of the case and the type of bronchial secretion formed, or because the volume of mucopurulent secretion produced is too great for normal methods of management. In such cases aerosol is the quickest and most efficient method of liquefaction of bronchial secretion.

The use of aerosol enzymes should be mentioned here for these have played a part in the development of this therapy. There is no question that proteolytic enzymes will cause the liquefaction of mucopurulent material, if brought into contact with this material by aerosol or instillation. However, it is the general experience that the complications are so severe and so frequent that this therapy has largely been abandoned. Inhalation of micro powders has likewise not been satisfactory in our hands and has resulted, in many cases, in increased irritation and uneven therapeutic effect.

The importance of additional liquid in the bronchial secretion must never be forgotten in treatment and this addition of liquid is an important function of aerosol therapy. It is for this reason that normal saline, used as an aerosol, is effective in a great many cases where bronchial secretion requires liquefaction. This is particularly true in the more acute cases and in those cases where the secretion is still liquid though of high viscosity. Clinical experience during the past five years has shown easing of cough and liquefaction of secretion with an aerosol of normal saline when a proper apparatus, capable of delivering a reasonably large amount of the aerosol, is used. With such an apparatus, the inhalation of aerosol normal saline for 30 minutes to one hour, several times a day, or constantly in a tent, will be as effective in properly selected cases as any medicated substance.

In chronic bronchial infections, asthma of long standing, emphysema and other long term bronchopulmonary conditions, a more difficult situation occurs. Several factors operate to increase both the amount and the viscosity of bronchial secretion. In addition, irritation is increased while bronchial drainage may be interfered with. Infection and irritation cause increase in secretion and eventually hypertrophy of mucous glands. Then

TABLE I

Number of Cases		96
Age	0 - 10	6
	11 - 20	5
	21 - 30	7
	31 - 40	18
	41 - 50	27
	51 - 60	21
	61 and over	12

cough becomes severe and bronchospasm accompanies it or is a result. Elimination of secretion decreases with bronchospasm causing more irritation, cough, spasm and, of course, more secretion. Retention often leads to greater viscosity, particularly in the smaller bronchi. In such a complex situation, a truly liquefying aerosol may relieve irritation, aid drainage, and thus act to decrease bronchospasm and inefficient cough.

Liquefying aerosols fall into four different classes determined by effectiveness. The first group, the least effective, is simple liquid. In this group is aerosol of water or normal saline, which is adequate in acute bronchitis and other conditions where the addition of liquid alone is all that is needed. When greater effect is necessary, a wetting agent or detergent is added. This was first suggested by Grace. The action now is depressing of surface tension with penetration of water into the mucus itself.

It is important to remember that the detergent is not mucolytic in any sense, and does not become so by placing such a label upon it. However, where addition of liquid to mucus can occur, a detergent aerosol will cause expectoration of bronchial secretion and decrease in severity of cough. Thus, the detergent containing aerosol makes up the second group, with a much greater effectiveness than saline or water alone. It is indicated in the more chronic case where mucopurulent secretion is tenacious and viscid, but still liquid enough to become thinner with addition of more liquid. The detergent aerosol solutions, available commercially, are in this group as regards effectiveness. They have, however, demonstrated two distinctly undesirable characteristics. First of these is pharyngeal and tracheal irritation, which is probably due to sodium bicarbonate. In several cases, this irritation was so severe that the aerosol had to be discontinued and one of normal saline substituted. The second is production of an opaque precipitate on tent canopies and premature beds, making it difficult to observe and manage patients. This seems to be caused by a combina-

TABLE II

Duration of Treatment	
1 week	11
2 weeks	21
3 weeks	12
1 month	20
6 weeks	5
2 months	10
3 months	9
4 months	3
5 months	2
6 months	3
TOTAL	96

tion of glycerin and sodium bicarbonate and raises the question of the actual need of these materials in an aerosol.

The addition of glycerin to maintain the stability of aerosol droplets was introduced by Abramson in 1940. Prigal (1947) did extensive work involving glycerin and propylene glycol in aerosols. This and later work showed the instability of water droplets and the stabilization of these by addition of glycerin. This work, while accurate, overlooks two important facts when applied to the problem of bronchial secretion.

The first is that if the inspired air is not saturated with moisture it is a tremendous advantage to saturate this from the aerosol rather than taking the liquid from the tracheo-bronchial mucosa. By so doing, the mucosa is protected from a drying effect which is in itself irritating and secretion is not further dried and thickened. Both of these occur when the liquid is maintained in droplets, even if droplets, once deposited, tend to reverse the drying.

The second fact relates to the circumstances under which the studies were done. It is true that, in an open atmosphere, water droplets of minute size evaporate, break up and disappear rapidly. However, in a closed system, such as the tracheo-bronchial tree, once the air is saturated, there is no longer any possibility that water will evaporate. Consequently, an aerosol of water or saline will maintain its droplet form in the bronchi, once the air is saturated. It would seem, therefore, that glycerin is unnecessary if proper aerosol equipment is used.

Aerosols containing detergents are effective in aiding liquefaction of mucus which is of high viscosity, but definitely liquid in form. Where speed is important, where the secretion is too thick or in cases where mucus is produced at too rapid a rate, another class of aerosols is needed. This is the third class, whose efficiency is increased by the addition of a material which aids solution and produces liquefaction of mucus. Potassium iodide (Levine, 1947) or ammonium chloride (Prigal, 1948) are easily used, being effective, non-irritating in proper dilution, and mix well with ordinary aerosol solutions. Potassium iodide is much the best solvent material. It is effective in dilutions of 0.1 per cent when given in adequate amounts. Ammonium chloride requires 10 per cent solution which is less efficient and more irritating than potassium iodide. Sodium bicarbonate is far down in the scale as a solvent and causes definite irritation.

Potassium iodide can be added to a detergent solution making an aerosol which offers liquid, detergent, and solvent at one time. Other materials

TABLE III

Continuous Therapy	
Oxygen Tent	60 hours
I.P.P.B.	48 hours—following five days intermittent
I.P.P.B.	4 months almost continuous (two-four oxygen cylinders a day)
I.P.P.B.	4 weeks

can be added as needed. Bronchodilating drugs can be used when indicated without interfering with any of the other actions of this aerosol. It is also possible to use antibiotics. Since retention of the antibiotic is important and detergent aerosols encourage bronchial drainage, we believe the two should be used as separate aerosols and at different times, rather than as a combined treatment.

The fourth class of liquefying aerosols is the truly digesting proteolytic substance. These are the enzymes which, when inhaled or instilled, change the characteristics of mucopurulent secretion in a short time. As stated above, these require careful and precise technique despite which complications may occur. If there were nothing else to use, the risk would be justified, but when such excellent results can be obtained by detergent aerosols of the second and third classes, little excuse exists for aerosol enzymes.

In bronchial disease, where the viscosity of mucopurulent or mucoid secretion creates a problem, an aerosol of the third class is the treatment of choice. Such treatment is indicated in chronic bronchial infections, asthma, emphysema, severe postoperative bronchopulmonary complications, acute tracheobronchitis in young children, etc. In some of these cases, there will be rapid liquefaction of mucus and expectoration will be liquid. In some, the mucus is rubbery and gelatinous in nature, whether because of inspissation or because it is secreted as a thick, almost solid material. Such mucus will not liquefy easily, but elimination is stimulated by a different process.

When these patients were first treated with the aerosol, they reported that they were coughing up "chunks" of sputum. On examination, this was almost solid mucus, frequently containing a few cells. However, its surface was more liquid, if only for a tiny distance. There was little doubt that more mucus was being expectorated with less effort than previously. The mechanism seems to be the liquefaction of the surface of such a solid piece of mucus. Because of the detergent, the liquid gets between the mucus and the mucous membrane and makes "shaking it loose" possible.

This is an important fact. It is not necessary to liquefy all mucus as long as the attachment or the apposition to the bronchial mucosa becomes less definite. When this occurs and there is no longer any adhesion, this material can be moved up in the bronchi more easily and expectorated without too much trouble. When the mucus has become truly inspissated

TABLE IV

RESULTS (MEASURED BY LIQUEFACTION OF SPUTUM AND EASE OF EXPECTORATION)

Excellent	66
Good	30
Fair	0
No Improvement	0
TOTAL	96

and is hard, there is little effect from the use of an aerosol until a fairly long time has gone by. In this type of case, we have found that such mucus, when left in a test tube full of a commercial detergent aerosol, remains almost unchanged after 24 hours. It is therefore idle to expect that a few minutes of inhalation or a long period of inhalation is going to cause a great change in the physical constitution of this material. However, when used in conjunction with other modes of therapy, a proper detergent aerosol may aid in shaking this material loose from its adhesion to the bronchial mucous membrane and aid in its expectoration.

From another standpoint, an aerosol can accomplish something that is done with more difficulty by the bronchial mucous glands themselves or when medication is given by mouth or parenterally which is expected to be excreted through these same glands. In the normal bronchus or in the bronchus which is the seat of an acute inflammation, there are a given number of mucous glands. This is changed in chronic bronchial disturbances. In bronchial asthma, chronic bronchitis and many other conditions where there is an excess demand for mucoid secretion in the bronchus, we find a tremendous increase in the number of goblet cells and in the distribution of mucus producing glands. These may be increased by volume as much as 100 times over the normal state. If the mucus produced by these glands is for any reason viscous, liquefaction cannot be easily accomplished by the giving of oral medication. Potassium iodide, for example, is effective in acute pathology and in the reasonably normal patient in dosages which approach 1 cc. at intervals during the day. If the number of mucous glands and their volume is increased many times, one would need 10 cc., 20 cc. or even 100 cc. of this substance to produce a similar concentration in all of the goblet cells for a therapeutic effect. This is obviously impossible because of the individual sensitivity to such drugs. However, it is possible to introduce potassium iodide as an aerosol in the concentration which is most effective in the bronchial lumen. Although the action is many times greater when the potassium iodide is present in the goblet cells during the actual formation of mucus, it still has a definite and noticeable liquefying action when administered as part of an aerosol. This is particularly noted in cases where the mucus is extremely thick and rubbery.

The actual physiologic changes which have occurred in bronchial function associated with this pathology can be alleviated in part by aerosol therapy. Irritation is present in all bronchial pathology. Whether it is caused by infection, by retained mucus, by cough, or by irritating agents which have been inhaled, a highly humidified inspired gas and additional

TABLE V

Evidence of tracheo-bronchial irritation	0
Evidence of iodism	0
Significant changes in blood count	0
Significant urinary findings	0
Bronchoscopic investigation after therapy	7
Post mortem examinations	3

moisture to the mucous membrane act to soothe and alleviate this irritation. Thus, one can expect that an aerosol, which is in itself non-irritating, can act to alleviate some of the irritation of the bronchial tree. If this is so, another important function can be accomplished. Irritation is responsible in part for bronchospasm which is such a commonly associated handicap in all bronchial disease. When irritation can be alleviated, spasm will be improved. Some of the bronchospasm is occasioned by the attempt to eliminate thick mucoid secretion. The greater the effort required to eject this material, the more the bronchus contracts and the greater the amount of spasm that occurs. Consequently, if the mucoid material is liquefied or even shaken loose, this again will act to decrease bronchospasm present. Likewise, improvement in irritation, improvement in bronchospasm, and ease of elimination of bronchial secretion act to decrease the violence and frequency of cough. Since cough is designed to eliminate undesirable matter from the tracheobronchial tree, its force and duration bears a direct relationship to the amount of irritation caused by the offending material and to the ease in eliminating it. Irritation and bronchospasm act to impair the efficiency of cough and thus create more violent spasms with less effect. With the improvement which aerosol is capable of causing, cough may be less vigorous and of less duration but of much greater efficiency. Thus, drainage may be increased and the airway kept clear with much less effort. As the material becomes liquefied, methods of drainage, such as postural drainage and the use of exsufflation with negative pressure, should be added to take advantage of the benefits resulting from this therapy.

One cannot expect a detergent aerosol to eliminate infection, improve asthma, change emphysema or have any effect on complete bronchial obstruction. When the bronchus is completely occluded, the aerosol will simply hit the surface of the obstruction and not penetrate further. When this obstruction is semi-solid mucus, the use of aerosol, combined with exsufflation with negative pressure, may be effective since eliminating a portion of the mucus obstruction may permit the entrance of the aerosol into the bronchus. Unless the complete obstruction is removed, this is impossible. Consequently, in the case of complete obstruction, one should use the detergent aerosol as an adjunct to other therapy and not expect it to do the job completely. If the obstruction is incomplete, the aerosol may aid in liquefaction. It has been our experience that exsufflation with negative pressure not only eliminates the obstruction more rapidly and

TABLE VI
DIAGNOSIS OF MAJOR CONDITION

Bronchiectasis	34
Asthma	27
Emphysema	22
Chronic Bronchitis	9
Acute Tracheobronchitis	4
TOTAL	96

more completely, but does so with less disturbance and effort on the part of the patient.

A new aerosol solution was obviously needed to accomplish all of the results mentioned. It would be in Class 3, containing liquid, detergent and a mucolytic chemical. One important point must be freedom from irritation, even over long periods, because in chronic disease extended treatment becomes necessary. Furthermore, an aerosol which is non-irritating to a normal bronchus, may react altogether differently in the hyper-irritable mucosa of asthma, chronic infection with bronchospasm, or emphysema. After careful investigation and study, an aerosol solution was made which will be referred to here as Aerosol Solution No. 2.

The detergent selected is Tergitol 08 (sodium 2-ethylhexyl sulfate). This was used extensively in concentrations of 0.25 per cent by Petroff in the treatment of tuberculous emphysema. No toxicity was observed in patients so treated. In addition to this and studies reported by Smyth and Hall, studies were done on rats, guinea pigs, rabbits and mice. These likewise demonstrated absence of toxicity and no disturbance of respiration in concentrations up to 0.25 per cent.

The use of potassium iodide in an aerosol brings up the question whether this is safe to use in known or possible tuberculosis. Lichtenstein and others have shown that potassium iodide may be given to tuberculous patients with safety. Even if there were deleterious effects when taken by mouth, the application by aerosol does not provide sufficient absorption to be significant. In this series, 22 patients who had known tuberculosis were treated with this aerosol over periods ranging from two weeks to six months. There was no evidence that it had any unfavorable effect on the tuberculous disease.

The aerosol solution was made to contain Tergitol 08, 0.125 per cent, potassium iodide, 0.1 per cent, in sterile water.* For the reasons previously stated, no glycerin or other material was used. This was administered to a group of 96 patients. No irritation or toxic effects were noted (Table V).

These patients had severe chronic or acute coughs and demonstrated thick tenacious viscid mucopurulent bronchial secretion. One characteristic that all these had in common was a spasmodic type of cough which produced noticeable dyspnea and in some cases, actual cyanosis. In all of them, a

TABLE VII
CASES WITH COMBINED PATHOLOGY

Bronchiectasis and Tuberculosis	18
Emphysema and Bronchiectasis	17
Asthma and Chronic Bronchitis	16
Asthma and Bronchiectasis	10
Asthma and Emphysema	9
Emphysema and Tuberculosis	4
Bronchiectasis and Pulmonary Fibrosis	4

*This solution, now known as Tergemist® was furnished by the Abbott Laboratories, North Chicago, Illinois.

wheeze was audible and rhonchi and sibilant rales were obvious in the chest before treatment had started. In order to eliminate rapidly clearing disease, all of these patients had previously received broad spectrum antibiotics for periods ranging from five days to two weeks before therapy had started. Potassium iodide had been administered by mouth for periods of three to four weeks in 50 per cent of the cases with only a moderate amount of improvement. N.C.G. and Elliott nebulizers were used in all except 12 cases who used DeVilbiss No. 40 nebulizer. The routine was four treatment periods of one half hour each, given daily. The volume of aerosol used daily varied from 12 to 25 cc. In four cases, therapy was maintained constantly for longer periods.

Table I shows the age distribution of these patients. It is noticeable that 63 per cent were over the age of 40. This is the time when coughs are most chronic and most difficult to handle. Six were children under the age of 10. The patients received therapy for varying periods of time. It is interesting that almost all of them claimed some improvement immediately after the first inhalation, but there was no objective evidence of decreased viscosity or ease of expectoration until approximately 24 hours after therapy was started. In many cases, where there was no obvious decrease of the viscosity of the secretion, patients stated that it was easier to raise and expectorate. This was such a common experience that it led to the investigation of the mechanism of liquefaction at the surface rather than completely through a particle of sputum. At the end of the first week of therapy, the sputum was definitely more liquid and expectorated easily without spasms of cough in all of the patients treated.

Case Histories

Case 1: C. J., Male, age 52. Had worked in foundry for 30 years. His chest showed extensive emphysema with moderate silicosis. He had long standing and severe bronchial infection with production of extremely viscid mucus that seemed to collect in the trachea in a fairly large amount before it was expectorated. Each morning, after he arose, he began to cough. He went into a severe spasm of coughing to the extent of becoming actually cyanotic. This continued until, with great spasmodic effort, he expectorated approximately one mouthful of thick, greenish yellow mucopurulent material which always was eliminated as one mass that did not break up into small portions. The size and volume of this mass was approximately 2 ounces and was the reason for the severe spasm and cyanosis. He was started on the Aerosol No. 2 solution on September 18, 1954. This was done in conjunction with IPPB apparatus which had been used for the previous month. Three cc. of aerosol were inhaled four times a day. He was instructed to use this aerosol immediately upon awakening in the morning, before attempting to get out of bed. In the first 24 hours no change was noted. At the end of the second day, he said it felt easier to cough up this "egg" of sputum, but no objective evidence of improvement was noted. By the fifth day it was apparent that while the sputum came up in the same quantity, cyanosis did not occur with the cough spasm and he expectorated this in several portions instead of as one lump. At the end of the first week, the decrease in viscosity was noticeable, although it still remained an extremely thick sputum. He was continued on this therapy until February, 1955. The cough continued, but was much decreased. The actual characteristic of the bronchial secretion changed. By the end of the second week, it was noticeably liquid and continued to become more so in the period that followed. At the end of one month, the expectoration was primarily in the morning and at night and accomplished without spasms of cough and with expectoration of liquid mucopurulent material. He was able to return to work by January 1, 1955. He insisted on using the aerosol three times a day, despite the obvious improvement in bronchial secretion. At no time was there evidence of irritation of mouth, throat, larynx, trachea or bronchi. The blood count showed no significant change during this period. Urine remained normal.

Case 2: R. W., Female, age 22. This patient was referred because of a diffuse and severe acute bronchitis. She was five months pregnant at this time. She showed

evidence of acute infection, temperature 102° F., almost constant cough with little expectoration. Breath sounds in all parts of her chest were completely covered by rhonchi and sibilant rales. She was given broad spectrum antibiotics. The temperature returned to normal in 24 hours, and all signs of toxicity disappeared. Antibiotics were continued for a period of four days. Although infection had been eliminated, neither the cough nor the physical findings changed to any extent. Expectoration was extremely difficult, following long spasms of cough, and the material was thick, stringy yellowish-green mucopurulent secretion. Aerosol No. 2 solution was started on November 23, 1954. An N.C.G. nebulizer was used, periods of treatment being one-half hour four times a day. This was continued for a period of 11 days when the chest was clear of secretion. She began to expectorate with noticeable ease on the third day of treatment, although, as was true in other cases, she claimed that the improvement began after the first 24 hours. Throughout the week, the expectoration of mucopurulent material increased in volume and occurred without the necessity of cough spasms. For the last two days of this treatment, there was little expectoration, and rhonchi and sibilant rales disappeared from the chest.

Case 3: R. G., Male, age 5. This child had bilateral bronchopneumonia involving areas in the lower half of both lungs and in the right upper lobe. He had been receiving antibiotics and oxygen for a period of two weeks intermittently before referral to the hospital. On admission, his temperature was 104.2° F. He was extremely dyspneic and showed cyanosis of the lips and paleness of the skin. His breathing was shallow with retraction of intercostal spaces and supra clavicular areas. Physical examination showed the chest to be full of rhonchi and sibilant rales that obliterated all other physical findings. He coughed frequently but did not expectorate mucus. He was placed in an oxygen tent into which aerosol was introduced by an N.C.G. nebulizer. This was allowed to run constantly for the first 24 hours. Following that, there was noticeable improvement in the physical findings in the chest. Rhonchi were still present, but were not as loud or as diffuse and breath sounds could be definitely heard. His respiration had decreased and was deeper at this time. Cyanosis did not appear once he was placed in the oxygen tent. During the second 24 hours of the same treatment the cough showed a change in type and sound. Although this child did not expectorate, the cough appeared to become much looser and there seemed to be secretion appearing in the throat which was swallowed. At 48 hours, rhonchi were no longer heard, although medium rales were elicited in both lower lobe areas. At the end of 60 hours, the aerosol administration was changed to intermittent treatment of one hour with equal rest periods between. Improvement continued and he was discharged to continue this therapy at home. At this time, the chest sounded relatively clear, although there was still some x-ray film evidence of pneumonic areas. Cough continued at intervals during the day and was more severe at night. At these times, evidences of secretion could be heard by auscultation. The program of one-half hour aerosol inhalation, four times a day, was instituted and he was placed on postural drainage. At the end of one additional week of this therapy, there was neither cough nor evidence of bronchial secretion. At no time did this child actually expectorate secretion, but it could be heard bubbling into the pharynx during episodes of cough. The blood count showed only a change from acute infection back to normal levels. There was no change in the urine.

Case 4: J. C., Male, age 52. This patient showed recurrent pneumonitis with severe cough. He expectorated fairly large amounts of thick tenacious mucopurulent secretion. On physical examination, rales and altered breath sounds were heard in both lower lobes, and rhonchi and sibilant rales were obvious all over the chest. Bronchoscopy demonstrated an acutely inflamed bronchial mucous membrane, reddened, edematous, and lined with tenacious secretion. This membrane bled easily on touch. The apertures of the bronchi of the third order were extremely narrowed by the edema and inflammatory reaction. He was placed on Aerosol No. 2 solution with an N.C.G. nebulizer. The period of treatment was one-half hour, four times a day. Approximately 25 cc. of solution was used in each 24 hours. This was continued for one month. During this time, there was a dramatic change in the quality of secretion, early in the treatment. The cough and expectoration became easier and the bronchial secretion liquid and easily eliminated by the end of the first week. Treatment was continued for one month when bronchoscopy was repeated. The mucous membrane appeared almost entirely normal and the bronchial apertures were normal. Cytological smears showed normal epithelial cells, and biopsy revealed normal bronchial mucosa.

Discussion

In this series, there was no evidence of bronchial, laryngeal or pharyngeal irritation and none of the patients was unable to tolerate the aerosol. Although ages ranged from five to 80, there was no noticeable difference

in the tolerance of the solution by the patients in different age levels, nor was there any evidence of iodism in any case. Table II shows the duration of treatment which extended in periods varying from one week to six months. Only four patients received treatment other than the routine intermittent method. This routine method was inhalation of the aerosol for one-half hour at a frequency of three to five times daily. These four patients received therapy over a period as noted in Table III. One case, No. 3, above, was a child in an oxygen tent. The other three were adults with extensive pulmonary pathology including interstitial pneumonitis, emphysematous blebs and cysts and extensive emphysema and lung destruction. These patients were on I.P.P.B. therapy with the Aerosol No. 2 Solution used in the nebulizer of the apparatus. After a period of intermittent treatment varying from five to two weeks, each of these patients, because of developing dyspnea, insisted on using the positive pressure apparatus constantly, even during sleep. The nebulizer was refilled every half hour. One used this therapy for 48 hours. Another used the apparatus constantly for four weeks. He had special nurses and refused to discontinue the constant use of pressure breathing. He used up four to six cylinders of oxygen a day and 3 cc. of aerosol solution every half hour, making a total of 144 cc. daily during this period. A fourth patient was in the same category and used two to three cylinders of oxygen daily with positive pressure breathing and aerosol over a period of four months. It was particularly noticeable that in none of these patients was there evidence of bronchial irritation and in all of them there seemed to be considerable relief of the cough and diminution of expectoration, although their dyspnea became worse and their breathing much more labored. Two of these patients came to post mortem. The report on the bronchial mucosa follows:

Post Mortem Studies

Case 1: Male, age 60. Congenital cystic disease, fibrosis of lung, bronchiectasis. Bronchogenic carcinoma noted on x-ray film one year before death. Aerosol solution—20 cc. daily—nine days before death.

Pathological Report, courtesy of Dr. Elie Leroy:

Carcinoma at base of right lung and right middle lobe and bronchus. Many lymph nodes. Superior vena cava compressed. Bronchial wall and mucosa replaced by grayish yellow homogeneous structure. Left lower lobe almost solid—gray and pink—tiny cysts. Most of the bronchi in the left lung showed no neoplastic involvement of the wall grossly.

Microscopic: Cystic cavities formed by dilated bronchi which were lined by tall cuboidal ciliated epithelium. Bronchial wall replaced by large masses of anaplastic cells.

Right lower main bronchus: mucosa missing in some areas and replaced by cords of dark staining cells varying greatly in size and shape. Bronchial wall completely replaced by these cells and only remnants of cartilaginous plaques noted. Left lower lobe: dilated bronchi lined by hyperplastic tall columnar epithelial cells.

Liver: carcinoma metastases; Spleen: congestion, and Kidney: nephrosis chronic (lower nephron).

Case 2: Female, age 44. Old tuberculosis with fibrosis and emphysema. Four months constant use of Aerosol No. 2, 10% cc. daily.

Pathological Report, courtesy of Dr. J. E. Habegger:

The tracheobronchial tree contains relatively little mucus. The lungs showed marked scarring, many cavities and bronchial communications. Lower lobes show nodular and fibrotic disease. Only a few cm. of aerated lung remained. The rest of the lung was either completely nodular, fibrosed or cavitary.

Microscopic: Bronchiolar epithelium is normal for some distance showing metaplasia and absence of lining as it enters tuberculous cavity. Respiratory bronchioles lined with low cuboidal epithelium. Right main bronchus appeared normal. Liver showed

moderate passive congestion of central areas. Spleen—slight congestion. Kidney cortex had normal appearance. Glomeruli are quite normal. Cytoplasm of proximal convoluted tubules is slightly swollen, evidence of slight post mortem change or mild cloudy swelling.

Case 3: Female, age 52. Severe asthma for nine years. Aerosol No. 2, one week intermittent treatment and 48 hours continuous therapy.

Pathological Report, courtesy of Dr. Elie Leroy:

The large bronchi of the right lung were found to contain large masses of mucoid material. The lining was reddish.

Microscopic: The large and small bronchi were filled with masses of mucoid material embedding desquamated epithelial cells and neutrophilic leucocytes. The lining of the large bronchi was formed by a squamous stratified epithelium. The epithelial cells had a vesicular nucleus and in some places they varied in shape and size. Many branches of the pulmonary artery were filled with organizing thrombi. In some of them there was recanalization of the thrombotic masses.

Liver: fatty degeneration; Spleen: hyperemia, and Kidney: arteriolo-sclerosis with necrosis. Nephrosis, acute.

Cause of death: 1) multiple pulmonary emboli—duration up to one month, 2) coronary sclerosis, acute heart failure (cor pulmonale) and 3) anoxia associated with chronic asthma.

Discussion

Examination of the bronchi following treatment was done in seven patients. In each of them, observation of the mucous membrane, biopsy and cytological smears were done. No evidence of bronchial irritation or damage attributable to the aerosol was found. Three were bronchoscoped before treatment and again following it. In all three there was decrease in inflammation and secretion following the aerosol.

It is particularly interesting to note the reports of normal or slightly changed bronchial mucosa in patients who had severe and long lasting bronchopulmonary disease. Here we would normally expect reports of extensive destruction and inflammatory changes in the bronchi as a result of the underlying disease. Such changes were found in two cases. We cannot say that any aerosol can actually change this pathology. The evidence does, however, suggest that, if irritation can be removed, the bronchial mucosa has wonderful powers of rapid improvement and recovery.

The absence of laboratory and histological evidence of toxic changes in other organs of the body is also worthy of note. This aerosol has met the requirements mentioned above of being non-irritating and non-toxic.

There was improvement in all of the 96 patients who used aerosol No. 2 solution. It is important to evaluate the part which the aerosol solution played in this improvement. Acute tracheobronchial inflammations may improve on aerosols of normal saline and antibiotic therapy may cause great changes in both cough and expectoration. This is more common in younger patients. In this series, only 11 were classified as acute and these were all in the under-30 age group. The remaining 85 were old, well established chronic infections that were causing trouble by reason of the viscosity of the bronchial secretion or because there was an acute flare-up of the infection. Seventy-six (89.4 per cent) of these cases were over 31 years old and 59 (70 per cent) were over 40. Table II shows the classification by pathology. The preponderance of emphysema, chronic asthma, and bronchiectasis indicated that these are the cases in which there are hypertrophic changes in bronchial mucous glands.

This, then, is a group of patients in which a class 3 aerosol is needed—liquid, detergent, and mucolytic chemical. In 12 cases, another detergent

aerosol was substituted without the knowledge of the patients. In each case, the patient complained that things were not as good as before. When aerosol solution No. 2 was replaced, the improvement was noted. Most of the patients, being ignorant of the substitution, attributed the change to weather conditions.

The aerosol No. 2 solution resulted in a more liquid sputum, more easily expectorated with less cough. With this beginning, bronchospasm was diminished and it was possible to maintain a free airway. Although most of the cases were so chronic that mucoid secretion continued to form in fairly large amounts, continuation of this therapy for as long as six months in the most difficult cases, kept the secretion liquid and drainage good. Since 88.5 per cent of the patients had been under treatment for long periods previously, the definite improvement would seem to be due to the aerosol solution. The particular combination of detergent (Tergitol 08—sodium 2-hexylethyl sulfate, 0.125 per cent), mucolytic chemical (potassium iodide 0.1 per cent) in sterile distilled water, seemed effective in this type of case.

SUMMARY AND CONCLUSIONS

1. Aerosol therapy is indicated when thick viscous mucopurulent secretion occurs in bronchopulmonary disease.

2. Its action and limitations in such cases is discussed, including the need of a liquefying aerosol.

3. In severe and chronic disease, an aerosol containing liquid, detergent and a mucolytic chemical is the efficient approach.

4. A new aerosol solution containing Tergitol 08 (sodium 2-hexylethyl sulfate) 0.125 per cent, potassium iodide 0.1 per cent in water is described.

5. A series of 96 patients with severe bronchopulmonary disease was treated by this aerosol solution. No irritation of mucous membranes or toxicity was noted.

6. Clinical results are reported: Excellent in 66, good in 30, fair none, no improvement, none.

7. This aerosol solution appears to be definitely beneficial in bronchopulmonary disease with thick viscous mucopurulent secretion.

RESUMEN

1. La aerosolterapia está indicada cuando existe secreción mucopurulenta viscosa y espesa en un padecimiento broncopulmonar.

2. Se discuten su acción y sus limitaciones incluyendo la necesidad de usar un aerosol con propiedades liquefacientes.

3. En las enfermedades severas, crónicas, el uso de un líquido con detergente y mucolítico químico es lo más eficiente.

4. Se describe una nueva solución que contiene Tergitol 08 (Sulfato de 2-hexiletil, sódico) .125 por ciento, yoduro de potasio 0.1 por ciento en agua.

5. Se trató una serie de 96 enfermos con enfermedad broncopulmonar severa con este aerosol. No se notó ninguna irritación de las mucosas ni toxicidad.

6. Se relatan los resultados obtenidos: Excelentes en 66, buenos en 30, medianos, ninguno y sin mejoría, ninguno.

Esta solución en aerosol parece ser francamente benéfica en la enfermedad broncopulmonar con secreción viscosa mucopurulenta.

RESUME

1. La thérapeutique par aérosols est indiquée dans une affection broncho-pulmonaire lorsqu'apparait une sécrétion visqueuse muco-purulente.

2. Les auteurs discutent l'action et les limites de ce traitement, et même la nécessité d'utiliser un aérosol liquéfiant.

3. Dans une atteinte chronique et sévère, un aérosol contenant un liquide détergent et un mucolytique chimique constitue un plan thérapeutique efficace.

4. Les auteurs indiquent une solution nouvelle d'aérosol contenant 0,125% de "Tergitol 08" (sulfate 2-Hexylethyl de sodium), 0,1% d'iodure de potassium, dissous dans de l'eau.

5. Une série de 96 malades atteints d'affection broncho-pulmonaire grave fut traitée par cette solution d'aérosol. On ne nota aucune irritation des muqueuses ni aucun signe toxique.

6. Les auteurs en rapportent les résultats cliniques: ils furent excellents chez 66 malades et bons chez 30.

7. Cette solution d'aérosol parait être vraiment favorable dans les cas d'affection broncho-pulmonaire avec sécrétion muco-purulente et visqueuse.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

1. Eine Aerosol-Therapie ist angezeigt, wenn bei bronchopulmonaler Erkrankung eine zähe, schleimig-eitrige Sekretion auftritt.

2. Ihre Wirkungsweise und Grenzen werden für solche Fälle besprochen, einschliesslich der Notwendigkeit eines verflüssigenden Aerosols.

3. Bei schwerer und chronischer Erkrankung ist ein Aerosol, das flüssige, reinigende und schleimlösende chemische Stoffe enthält, ein wirksamer Behandlungsweg.

4. Beschreibung einer neuen Aerosollösung, die Tergitol 08 (Natrium 2-hexyläthylsulfat) 0,125%, Jodkali 0,1% in Wasser enthält.

5. Eine Reihe von 96 Kranken mit schwerer bronchopulmonaler Erkrankung wurde mit dieser Aerosollösung behandelt. Es wurde keine Reizung der Schleimhäute oder eine Giftwirkung bemerkt.

6. Es werden klinische Ergebnisse wiedergegeben: Ausgezeichnete Wirkung bei 66, gute Wirkung bei 30, ohne Wirkung bei keinem Patienten.

7. Diese Aerosollösung scheint bei bronchopulmonaler Erkrankung mit zäher, schleimig-eitriger Sekretbildung entschieden heilsam zu sein.

Sputum Cytology in Patients Following Enzyme Aerosol Therapy*

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Introduction

The problem under consideration in this paper deals with two techniques, sputum cytology and pulmonary enzyme aerosol therapy, which have come to the fore in the last decade. In order that their significance may be better understood, the paper will begin with a brief history of the two procedures. The relatively new technique of sputum cytology has afforded a simple but accurate method for the diagnosis of pulmonary malignancies as well as other respiratory diseases, asthma and fungus diseases being two outstanding examples. Aerosol therapy, applied to the pulmonary tree, has been in existence somewhat longer and has been used widely with much success. Of late two enzymes, trypsin and dornase (desoxyribonuclease), have been utilized in an attempt to treat chronic lung diseases more successfully. This technique has been employed by a small number of groups and the clinical success has been questionable thus far. In addition, Farber and associates[1] noticed evidence of atypical metaplastic changes in sputum of patients following trypsin and trypsin plus dornase aerosol, which must be evaluated before the technique is used widely. As yet cytologic changes following dornase aerosol alone have not been evaluated by this group and it is this problem with which I will be concerned in the present paper.

History of Pulmonary Cytology

Cytologic investigation of sputum has proved to be an invaluable aid in the diagnosis of pulmonary diseases, particularly in reference to pulmonary carcinoma. It was not until the latter part of the nineteenth century that much effort was directed along these lines. However, as early as 1843, Walsche[2] reported gross particles of malignant tumor in the sputum. The microscopic discovery of tumor cells in the sputum was first reported by Beale[3] in 1860. The finding was made in a patient with carcinoma of the pharynx. The first report of a series of cases was made in 1918 by Hampeln.[4] He found malignant cells in the sputum of 13 out of 25 patients with bronchogenic carcinoma. Both of these observers used unstained sputum.

Sputum can be studied in two manners: (1) by the ordinary histologic methods consisting of fixing buttons of sputum and sectioning, and (2) by smearing sputum and examining. There were reports of good results made by investigators using the former method, but this mode of examination has several important weaknesses, resulting in the almost universal use of the smear technique in sputum cytologic analysis.

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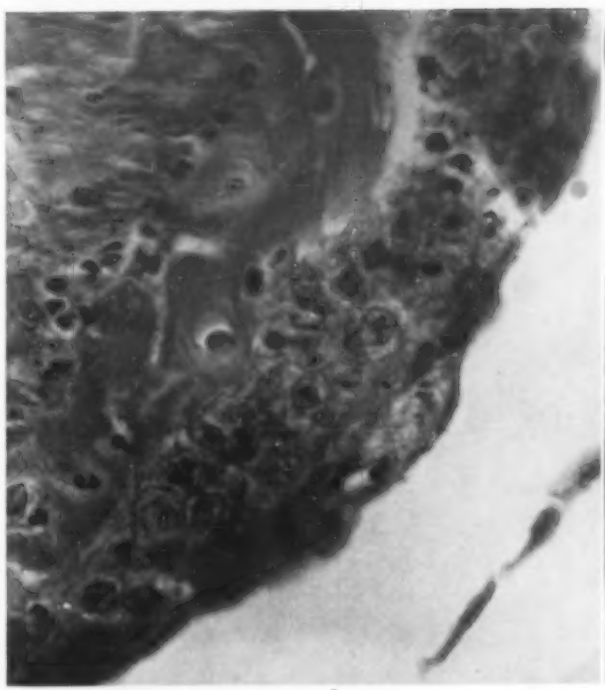

FIGURE 1

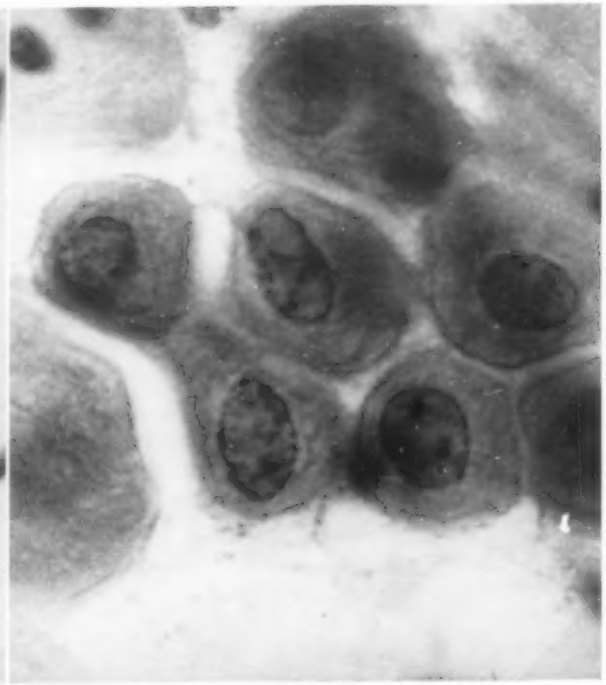

FIGURE 2

Figure 1: A section of bronchial epithelium showing an area of squamous metaplasia which occurred in a patient following treatment with an aerosol solution of trypsin. (× 2880).—*Figure 2:* Atypical metaplastic cells seen in cytologic smear of the sputum of the patient in Figure 1. (× 4506).

As has been noted previously, the earlier observers used smears of unstained sputum and were only able to pick out cells and cell groups, which were extremely bizarre. Therefore, methods of fixing and staining had to be developed in order that the nuclear and cytoplasmic characteristics of cells could be studied. Several methods of fixation and staining were tried and of these, two have persisted. Dudgeon and Wrigley[5] published a report on the finding of carcinoma cells in the sputum of 39 out of 58 possible cases of bronchogenic carcinoma. They used a method which the former had developed earlier. Schandinn's solution was the fixative and hematoxylin and eosin was the stain. Papanicolaou and his associates developed probably the most popular method of fixing and staining sputum smears. This method consisted of fixing with equal parts of alcohol and ether and staining with a compound stain developed by himself. The procedure was not adopted until 1943, when he published a monograph[6] on examination of vaginal secretion in the diagnosis of uterine carcinoma.

In the last two decades reports have been made on large numbers of cases with high results. Wandall[7] in 1944 found tumor cells in 84 out of 100 (84 per cent) cases of bronchogenic carcinoma; he used the Dudgeon method. He further reported the finding of malignant cells in the sputum of 37 out of 69 cases in which bronchoscopy was negative for biopsy, thus illustrating the value of the relatively simple method of sputum cytology for diagnosis. In the last decade many workers have used the Papanicolaou method to good advantage. Farber, Benioff and McGrath published two papers, one in 1949[8] and the other in 1951,[9] in which they were able to report 90 per cent positive results, when five or more samples of sputum were used. When fewer samples are examined, the accuracy declines sharply. Thus the accuracy of sputum diagnosis has proved to be great.

History of Aerosol Therapy

Therapy in pulmonary disease has been carried out for a long time in non-specific fashion, as far as anatomic site of action is concerned. Drugs are given by such general routes as oral, intra-muscular and intravenous and their distribution is throughout the entire body, rather than concentrating at the site of the disease process. In addition, often in chronic pulmonary disease, e.g., chronic bronchitis, bronchiectasis, etc., the therapeutic agents are not effective because they are unable to penetrate into the diseased area. It was then thought that one could better solve the problem through the topical use of drugs, directly in the bronchial tree. For this purpose aerosol therapy has been developed and utilized.

Aerosol therapy was first studied by Heubner[10] in 1919. He reported the successful use of 1:100 epinephrine aerosol in mild to moderately severe bronchial asthma with minimal systemic effects and immediate results. With the advent of antibiotics many reports appeared on the use of aerosol antibiotic therapy. Bryon, Sonsome, and Laski[11] first used aerosol penicillin in man with chronic pulmonary disease. Good concentration was possible here, but one had the ever present danger of allergic reaction, which could be severe. In 1946 Olsen[12] published his work on the successful

use of streptomycin aerosol therapy. He also combined penicillin and streptomycin.

So far we can see that through aerosol therapy, investigators have applied drugs as epinephrine to control the spasm of bronchioles in asthma, and antibiotics have been used to control or destroy bacteria in the pulmonary tree. However, much trouble is encountered in diseases such as bronchiectasis, asthma, tuberculosis, etc. in which one deals with copious, heavy, often viscid sputum. It is in reference to this last mentioned problem that enzyme aerosol therapy has been investigated in the last few years. Particularly trypsin and desoxyribonuclease have been utilized thus far. The principle is obvious: digestion of the sputum, thus making it thinner and easier for the patient to expectorate.

The first group to use enzyme aerosol therapy was Limber, Roettig and Curtis.[13] They reported their work in 1952 in a paper entitled "Enzymatic Lysis of Respiratory Secretion by Aerosol Trypsin." These investigators used crystalline trypsin (Tryptar). No deleterious effects followed its use in preliminary studies with rabbits. They then reported on 33 patients, who had been given 251 treatments and noted thinning of sputum, thus promoting expectoration. The only side effects noted were some dyspnea, chills, and fever in a few patients. In 1954, Salomon, Herchfus and Segal[14] published a report on the successful treatment of 35 patients with aerosol desoxyribonuclease (pancreatic dornase). The results were good in general, being excellent in many cases. The diseases least helped were chronic bronchial asthma and emphysema. No side effects were noted here and no post-aerosol cytologic changes were observed. Farber, Gorman, Wood, Grimes and Pharr[15] reported in 1954 on the aerosol use of trypsin and trypsin plus dornase in pulmonary disease, tuberculosis being the chief disease process. The reports are far less encouraging than the reports mentioned previously. Trypsin alone was less effective than trypsin combined with dornase. The latter reduced cough and lessened sputum viscosity in most cases. Many severe side reactions such as fever, chill, dyspnea, urticaria, and hemoptysis were encountered. In addition cytologic changes were noted which persisted long after therapy was stopped. These changes consisted of atypical bronchial metaplasia and dyskeratosis, occurring in 12 out of 16 treated patients and persisting over six months after cessation of therapy. In fact, in some cases the atypical cells seemed to be increasing in number.

Trypsin and Desoxyribonuclease

Trypsin is a proteolytic enzyme contained in the exocrine secretion of the pancreas. In the last 20 years, the enzyme has been obtainable in pure crystalline form. The enzyme has been found to catalyze the following reactions: (1) conversion of chymotrypsinogen to chymotrypsin; (2) autocatalytic conversion of trypsinogen to trypsin; and (3) digestion of denatured and native proteins. It is assumed that trypsin digests protein by breaking up peptide bonds.

Desoxyribonuclease is the second enzyme under consideration in this paper. This enzyme acts upon desoxyribonucleoproteins. Desoxyribonu-

clease can be obtained in pure crystalline form from beef pancreatic extracts. The desoxyribonucleoproteins are largely responsible for the viscosity of sputum, particularly purulent sputum.[15] The pancreatic dornase acts by depolymerizing the desoxynucleoproteins, rather than digesting the proteins themselves.[14]

The action of trypsin and dornase on pus of different origins was studied and it was found that pus from tuberculosis cavities was acted on best by trypsin, because of the high concentration of fibrin. Dornase was more effective, however, on the pus of non-tuberculous origin, because the viscosity is largely due to the desoxyribonucleoproteins.[14] In a report in 1953, Swift[16] noted the effect of enzymes on nuclear staining. He stated that when proteins and nucleic acids are together in the nucleus, the acids join to the basic group on the proteins, making the two unstainable. However, there is an increased staining with acid dyes if the nucleic acids are removed by a nuclease as desoxyribonuclease. Also, the same holds true if the proteins are removed by an enzyme such as trypsin. Thus the nuclei of cells, when acted upon by either enzyme, would stain more densely.

This paper is concerned with the bronchial cellular changes following enzyme aerosol therapy. Consequently it would be necessary to know the actual response of the living organism to trypsin and dornase, from a biochemical as well as a cytologic point of view. Unfortunately the literature contains only a few isolated reports of gross observations. There are no reported studies concerning the chemical changes brought about by trypsin or dornase.

Animal Work

Previous to the use of enzyme aerosol therapy in humans, the drugs, trypsin and dornase, were given to animals in order that the effects of the enzymes on the bronchial tree and lung tissue could be evaluated. Strain A mice were used for this purpose. The strain was chosen because of its high incidence for the development of spontaneous and chemically induced pulmonary tumors. After 18 months 90 per cent develop tumors spontaneously.[17]

The following experimental material is the result of work done several years ago by Farber and associates.* Results of their work are included in this paper, with their consent.

TABLE I
PILOT STUDY

	Number of Animals	Number Developing Tumors	Percentage
Control	36	5	14
Trypsin	10	3	17
Dornase	18	7	41

*Dr. S. Farber, University of California, Cancer Research Division, San Francisco County Hospital.

Two month old mice were used for the experiment. A pilot group of 72 mice was used as a preliminary study to investigate whether or not further studies would be feasible. At six months of age, the strain A mice have an expected spontaneous pulmonary tumor incidence of 17 per cent.[17] The results of the pilot study are shown in Table I.

Thus the results of the preliminary study indicated that there is an increased incidence of pulmonary tumor following dornase aerosol and no increase following trypsin aerosol. The group is too small, however, to be totally significant. Therefore, following the pilot study, an expanded study was carried out in which 610 strain A mice were used. The results are below.

TABLE II[18]
SACRIFICED AT SIX MONTHS OF AGE (220 ANIMALS)

	Number of Animals	Length of Treatment	Number of Tumors	Percentage
Control	50	.....	10	20
Control with PO_4 Buffer	50	10 weeks	11	22
Trypsin	50	10 weeks	9	18
Dornase	70	10 weeks	21	30

TABLE III[18]
SACRIFICED AT NINE MONTHS OF AGE (240 ANIMALS)

	Number of Animals	Length of Treatment	Number of Tumors	Percentage
Control	70	.....		
Control with PO_4 Buffer	50	23 weeks	48	40
Trypsin	50	23 weeks	15	30
Dornase	70	23 weeks	33	47

One can now see from the expanded study that there is a significantly increased incidence of pulmonary tumor in strain A mice following dornase aerosol therapy. At the same time, however, there is no increased incidence following trypsin aerosol therapy. Cytologic and pathologic studies revealed no evidence of bronchial metaplasia in any of the mice.

Human Aerosol Studies

The clinical material to be referred to below was collected by Farber and associates at the San Francisco County Hospital. Their work with trypsin and trypsin plus dornase aerosol has been published.[15] These workers exposed 23 patients to dornase aerosol alone. They made smears of sputum before, during, and after enzyme aerosol.

The enzymes were given to patients by means of nasal aerosol inhalations. Initially the oral route was utilized but too much irritation resulted. The nose acts as a baffle and thus the larger droplets are prevented from reaching the pharynx, larynx, and trachea. First trypsin (Tryptar) was given, then trypsin plus desoxyribonuclease, and finally a group of patients received desoxyribonuclease alone in various phases of the larger project.

The first study consisted of the trypsin and trypsin plus dornase administrations. There were 24 patients in this series. The primary disease was pulmonary tuberculosis. Some had secondary conditions. Of these patients, seven were given trypsin alone and the remaining 17 received trypsin plus dornase. In the latter group, however, trypsin was administered constantly with periodic small doses of additional dornase. We see, therefore, that trypsin was the enzyme most used in this study. Sixteen of the 24 were studied cytologically and the results were published by Farber and associates.[15] These 16 patients had received both enzymes.

Of the 16, 12 showed typical and atypical metaplasia, discrepancy of maturation, and dyskeratosis. The cells showed cytoplasmic hyperkeratinization and relative enlargement of the nuclei. In addition, the nuclei were often irregular, with some increase in the prominence of the nuclear membrane. Some clumping of the chromatin was seen with a general increase in nuclear staining. Often cellular vacuolation was present.[18] Examples of these changes are illustrated in Figures 1 and 2. The above constituted the main cytologic changes. No lysis was seen on microscopic examination of the sputum at any time during the course of therapy. There was a moderate increase in macrophages and inflammatory cells for a short time following a specific pattern. This was not marked, however, and was transient.

In the second study, 23 patients were given aerosols of desoxyribonuclease. They all had tuberculosis as a primary disease. Several had associated conditions. The enzyme was given in a dosage of 20,000 units per day; the length of treatment varying from 12 to 42 days. There are 15 men and eight women in this study, most of whom are between 38 and 65 years of age. One died on the 21st day of treatment; a second left the hospital early in the study; and a third was found to have bronchogenic carcinoma, in addition to the primary disease of tuberculosis. Therefore, cytologic studies of their sputum will not be reported.

Sputum specimens were taken for several days prior to aerosol therapy in order to evaluate the pre-aerosol sputum picture. This is essential because in chronic pulmonary disease, such as tuberculosis and bronchiectasis, one often finds metaplastic cells and some degree of dyskeratosis and discrepancy of maturation. Smears were continued at periodic intervals throughout aerosol therapy and then at wider intervals for six to 18 months following the cessation of aerosol treatment. It is this series of slides with which I have been concerned.

TABLE IV
SUMMARY OF POST-DORNASE AEROSOL CHANGES

	Number of Patients
No Change	13
Transient Increase in Post-aerosol Metaplasia	5
Persistent Increase in Post-aerosol Metaplasia	2
TOTAL	20

Table IV is a summary of the results of my examination of the slides. In seven cases a post-aerosol increase in metaplasia was seen, but in five of these the picture returned to the pre-aerosol state quickly. In the remaining two cases metaplastic changes, both typical and atypical persisted but did not increase in amount. Several cases show pre-aerosol as well as post-aerosol atypical metaplasia with no increase in the latter.

The metaplasia was considered to be atypical when there was an irregularity in the shape and size of nuclei and an anisocytosis in cell groups. In typical metaplasia one would expect to see more regularity. Dyskeratosis and discrepancy of maturation followed typical metaplasia in amount. Dyskeratosis indicates the presence of an immature nucleus surrounded by a mature cytoplasm. Discrepancy of maturation refers to the presence of more mature cells mixed with immature cells in the same group, where the state of development should be uniform.

Six cases developed a transient post-aerosol eosinophilia. This probably indicates an allergic reaction to the enzyme.

Discussion and Conclusions

It has been the object of this paper to consider the cytologic changes resulting from trypsin aerosol therapy and to establish whether or not such changes would result from aerosol therapy with desoxyribonuclease.

As has been seen earlier, strain A mice were given aerosols of trypsin and dornase, with an equal number used as controls. The results uniformly showed an increase in bronchogenic tumors following dornase aerosol but no increase following trypsin aerosol. In addition, it was observed that there was no evidence of metaplasia in animal lung sections.

The next study consisted of the administration of trypsin plus dornase to humans. It was found that 12 out of 16 patients examined cytologically showed the development of persistent atypical metaplasia. In most cases the metaplasia increased with time. The major drug used in this series was trypsin and the conclusion at this time was that trypsin was the etiologic factor.

In the final study, 23 patients were given dornase aerosol. When these cases were screened and the results charted, it was seen that only two out of 22 patients examined cytologically showed persistent increase in atypical and typical metaplasia. Others showed only transient post-aerosol increase in metaplasia. An interesting observation in at least five cases was the pre-aerosol presence of "atypical" metaplasia.

It is of significance to note the difference in the results following aerosol therapy in mice and in man. In the former, dornase was the agent active in providing a tumor increase. In man, however, trypsin appears to cause significant post-aerosol changes. The atypical metaplasia, even though it is bizarre at times, cannot be called neoplastic but seems to fall somewhere between metaplastic and neoplastic type cells. The persistent changes following dornase aerosol were found in two cases out of 22 but these are only slight and the atypia is not great, as in those following trypsin aerosol.

In a paper referred to earlier by Habeeb and associates, the post-trypsin-aerosol cytologic changes were re-evaluated. No cytologic changes were detected in that study, however. The authors concluded that the therapeutic procedure, on the basis of their findings, was safe. On the basis of the illustrations which they published, their criteria for metaplasia do not meet accepted standards. An example of typical metaplasia, pictured by these authors, appears to be a normal mature squamous cell. In addition, the findings of Farber and associates cannot be disregarded. The post-trypsin changes are bizarre, showing a marked increase with time. It would seem that the changes following trypsin aerosol are real and significant, and careful observation of the patients showing the persistent metaplasia is necessary before further trypsin aerosol are real and significant, and careful observation of the patients showing the persistent metaplasia is necessary before further trypsin aerosol therapy is attempted.

The sputum changes following dornase aerosol are far different from those seen with trypsin. Most cases showed no increase in metaplasia and all but two that showed any increase, quickly returned to the pre-aerosol state. The presence of metaplasia in chronic pulmonary disease is not surprising and the transient increase in the sputum of metaplastic cells probably resulted from enzyme debridement of already present metaplasia. In the two cases showing persistent changes, the metaplastic increase was only slight and demonstrated no progressive post-aerosol increase. Since in the majority of human cases, no persistent post-dornase-aerosol metaplastic changes were seen, and in the two showing slight changes the significance is doubtful, it may be concluded that the therapeutic procedure of dornase aerosol therapy, in the absence of further cytologic evidence, can be considered seriously for further therapeutic trials.

SUMMARY

1. Sputum cytology has afforded a relatively simple but accurate method for diagnosis of bronchogenic carcinoma.

2. Pulmonary enzyme aerosol therapy utilizing trypsin and desoxyribonuclease has been reported upon recently with good clinical results. The effect is digestion and thus thinning of sputum, making expectoration easier.

3. A recent report from San Francisco by S. M. Farber and associates demonstrated the appearance of atypical metaplasia following trypsin and trypsin plus dornase aerosol. They exposed 23 patients to dornase aerosol alone and collected sputum smears before, during and after treatment.

4. These slides were examined by the author and the results presented and discussed in this paper. No atypical metaplasia was seen following dornase aerosol.

RESUMEN

1. La citología de esputo ha proporcionado un método simple pero preciso para el diagnóstico de carcinoma broncogénico.

2. La terapia pulmonar de aerosoles enzimáticos utilizando tripsina y desoxiribonucleasa se ha reportado recientemente con buenos resultados clínicos. El efecto es la digestión y por tanto la fluidificación del esputo, facilitando la expectoración.

3. Un reporte reciente de San Francisco por S. M. Farber y colaboradores demonstraron la aparición de una metaplasia atípica después de la administración de aerosol de tripsina y tripsina más dornasa. Expusieron 23 pacientes a aerosol de dornasa solo y tomaron frotes de esputo antes, durante y después del tratamiento.

4. Tales laminillas fueron examinadas por el autor y los resultados se presentan y se discuten en este trabajo. No se observó metaplasia atípica subsecuente al aerosol de dornasa.

RESUME

1. L'étude cytologique des crachats reprèsente une méthode relativement simple mais valable pour le diagnostic du cancer bronchique.

2. Récemment, on a rapporté les bons résultats cliniques obtenus par l'utilisation de trypsine et de desoxyribonucléase. Leur action sur la digestion des crachats et par conséquent leur fluidification favorise beaucoup l'expectoration.

3. Un travail que viennent de publier à San Francisco S. M. Farber et Collaborateurs, fait état de l'apparition de métaplasie atypique à la suite d'administration d'aérosol de trypsine associée ou non à la dornase. Ils ont soumis 23 malades à des aérosols ne contenant que de la dornase et en ont recueilli des frottis des expectorations avant, pendant et après le traitement.

4. Les lames ont été examinées par l'auteur de cette communication qui en montre les résultats et les met en discussion. Aucune métaplasie atypique n'apparut après les aérosols de dornase.

ZUSAMMENFASSUNG

1. Die Sputum-Zellkunde hat eine relativ einfache, aber genaue Methode geliefert für die Diagnose des Bronchial-Carcinoms.

2. Kürzlich wurde berichtet über die pulmonale Enzym-Aerosol-Therapie mit Benutzung von Trypsin und Desoxyribonuclease mit guten klinischen Ergebnissen. Die Wirkung ist eine Verdauung und damit Verdünnung des Sputums, wodurch die Expectoration erleichtert wird.

3. Ein kürzlich erschienener Bericht aus San Francisco von S. M. Farber u.a. demonstrierte das Auftreten einer atypischen Metaplasie nach Aerosol mit Trypsin und mit Trypsin mit Dornase. Sie setzten 23 Patienten einem

Aerosol mit Dornase allein aus und sammelten Sputumproben vor, während und nach der Behandlung.

4. Diese Ausstriche wurden vom Verfasser geprüft und die Ergebnisse in dieser Veröffentlichung vorgelegt und besprochen. Es konnte keine atypische Metaplasie nach Dornaise Aerosol beobachtet werden.

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Cor Triloculare Biatriatum

COMBINED WITH ATRESIA (OR HYPOPLASIA) OF THE MITRAL VALVE AND OF THE ASCENDING AORTA

Report of Two Cases with Transposition of the Great Vessels. Discussion of Related Embryology and Physiopathology.

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Although generally attributed to Holmes, the first observation of cor triloculare biatriatum was in actual fact reported by Chemineau in 1699.[1]

Such a malformation is relatively rare and if uncomplicated may not greatly impair either the aeration of blood in the lungs or the cardiac function in general, so that the syndrome may remain undiagnosed and even allow the patient to reach a mature age.

Barry and Isaac[2] have reported a case in an adult and collected six more in the literature, in which the youngest attained 14 years and the oldest 56 years of age, the latter case was reported by Mehta and Hewlett.[3]

Abbott[4] out of 1000 cases of congenital cardiac diseases found 42 instances of cor triloculare; 15 were bi-ventricular and 27 bi-atrial. The cor triloculare biatriatum constituted the primary lesion in 13 cases; additional defects occurred in the remaining 14.

Conn, Clark and Kissane,[5] reviewing the literature in 1950, brought the total of reported cases of cor triloculare biatriatum to 55. Since 1950 at least 17 additional cases have been described.† The cor triloculare biatriatum (C.T.B.-a) is quite often associated with other cardiac defects and such a combination is generally responsible for early death. The most usual concomitant malformation is the transposition of the great vessels.[6, 7, 8] Next in frequency are associated atresia or hypoplasia of one A-V orifice and the hypoplasia or atresia of one of the great vessels.

Brockman[9] collected from the literature 48 cases of mitral atresia (five cases from Abbott's and one original observation were included) and out of 42 of these, wherein particulars were available, found 33 instances in which the interventricular septum was either defective or missing (C.T.B.-a).

Among Abbott's 1000 cases of congenital heart disease there were 11 of aortic stenosis and 12 of aortic atresia. In almost all of them the aorta

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†References regarding said 17 cases are not given at this point since this paper is not a statistical report and it is quite likely that additional cases were overlooked.

became of normal caliber beyond the ductus arteriosus Botalli.

Brockman[9] found the association of aortic atresia or hypoplasia in 21 out of the 42 cases of mitral atresia he reported.

Rogers and Edwards,[8] after stressing that in the vast majority of C.T.B.-a. the great vessels are transposed, have suggested designating this malformation as type 1, and designating as type 2 those cases in which the great vessels are normally placed. The further classified group 1 into four subtypes, according to the relationship of the great vessels to the outflow portion of the common ventricle, namely:

A) the outflow tract is subdivided and it forms a narrow subaortic channel;

B) the outflow tract is subdivided and constitutes a narrow subpulmonary channel, a stenotic pulmonary trunk, or a subpulmonary fibrous stenosis;

C) the outflow tract is split into stenotic subaortic and stenotic subpulmonary channels of equal dimensions;

D) the outflow tract does not subdivide.

Cases of C.T.B.-a. of Rogers and Edwards' type 2 (without transposition of the great vessels) are extremely rare. Drey et al[7] reported a case of this kind and stated that theirs was the second example ever described. Rogers and Edwards[8] found a similar case from a collection of nine cases of C.T.B.-a. of the Mayo Clinic.

Two cases of cor triloculare biatriatum with transposition of the great vessels of the type, 1,A of Rogers and Edwards are herein presented.

FIGURE 1

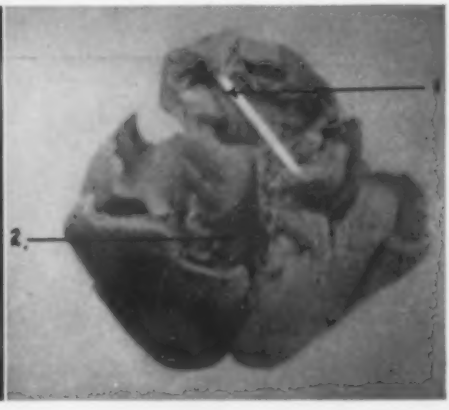

FIGURE 2

Figure 1 (Case 1): Antero-posterior roentgenogram of the chest showing the heart displaced to the right, the dextroposed aorta, the enlarged pulmonary artery, a left double contour (enlarged left atrium and single ventricle) and the dense hilar shadows. Diffused marked haziness of lung fields, especially at the right.—*Figure 2* (Case 1): Photo of the antero-superior aspect of the heart, showing the enlarged left atrium (1), and the single ventricle (2).

Both cases were complicated by other analogous cardiac defects: at the level of the mitral orifice (atresia in the first case and hypoplasia in the second) and of the aorta (hypoplasia in the first and atresia in the second).

Furthermore in the first instance a premature closure of the foramen ovale had occurred and an abnormal development of the pulmonary veins coexisted to make the anatomical picture still more varied.

Case 1: Baby D. (Hosp. No. 54-4000). The patient was a full-term white female infant born at Misericordia Hospital on August 17, 1954. This was the mother's first pregnancy described as normal throughout and devoid of any viral disease. A slight dyspnea and cyanosis were noted at birth, and the infant was placed in oxygen. When examined by the pediatrician about one hour after birth, the significant findings were: 1) moderate cyanosis and dyspnea; 2) sinus tachycardia with a rate of 140-160; 3) no cardiac murmur; 4) weak radial and femoral pulses; 5) breath sounds came through poorly and a few fine crackling rales were present. A diagnosis of persistent atelectasis of the newborn was made. Four hours later the general condition became worse; the cyanosis increased and the dyspnea was more pronounced; a rough systolic murmur was heard over the precordium, and the liver edge became palpable. A roentgenogram of the chest (Figure 1) revealed the cardiac shadow displaced to the right, a dextroposed aorta and an enlarged pulmonary artery. A double left contour and dense hilar shadows were also noted and the lung fields were markedly hazy, especially the right one. Despite all therapeutic measures employed (oxygen, tracheal suction, penicillin) the infant expired 16 hours after birth.

*Autopsy Findings**

A) *Heart*

The heart appeared enlarged with dilation and hypertrophy of the right auricle. The superior and inferior venae cavae entered the right auricle normally. The tricuspid valve appeared normal and opened into a truly single ventricle which was moderately hypertrophic. The pulmonary valve was normal. The pulmonary artery left the ventricle from its anterior surface. It arose from a slightly enlarged basal ventricular

*The autopsy was performed by the pathologist, Dr. G. Hatzel.

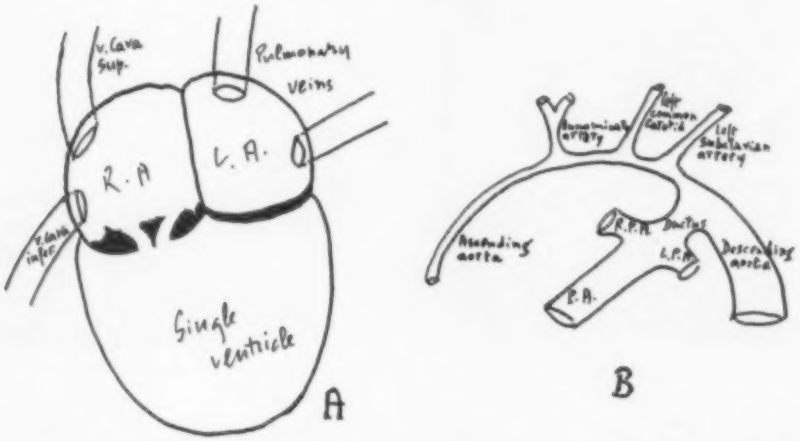

FIGURE 3 (Case 1): Diagrams showing: A) the atresia of the mitral orifice, the single ventricle and only two pulmonary veins entering the left atrium. B) The hypoplastic ascending aorta and the ductus arteriosus.

pocket. The artery was dilated but normally situated; 2 cm. from its origin, two vessels 5 millimeters in diameter (the right and the left pulmonary arteries) arose from the main artery in the normal fashion and entered the respective lungs.

The ductus arteriosus was very short (8 mm.) and patent. The ductus met the aorta at the normal point after the arch. The aorta beyond the entrance of the ductus arteriosus was normal. The aorta originated from the upper part of the base of the single ventricle. It lay anteriorly and to the right of the pulmonary artery. The aortic orifice had a calibre of 1 mm. The cusps of the valve were so hypoplastic that they could only be recognized with difficulty. The ascending aorta and the arch were of minimal internal diameter (1 mm.), and therefore of no functional importance. The coronaries, the innominate, the left common carotid and the left subclavian arteries departed from the hypoplastic aorta in the normal sequence, and were of normal calibre.

Only two pulmonary veins reached the left atrium—one from each lung. The left atrium appeared greatly dilated (Figure 2). The foramen ovale was closed. There was no sign of the mitral valve. It appeared as if there were no way whatsoever for the blood to leave the left auricle; and in fact, the cavity was full of clots (Figure 3).

B) *Lungs*

Edema fluid filled both lungs: numerous small patches of atelectasis were noted.

C) *Urinary System*

A stenosis of the right ureter at the junction of the inferior and middle thirds was present.

Anatomical Diagnosis

1) Cor Triloculare Biatriatum with transposition of the great vessels (type 1,A).
2) Severe aortic hypoplasia.
3) Mitral atresia.
4) Premature closure of the foramen ovale.
5) Anomalous development of the pulmonary veins.
6) Atelectasis of the newborn.
7) Stenosis of right ureter.

Case 2: Baby S.* A white female infant born on August 6, 1945 after a normal first pregnancy and full-term forceps delivery under ether anesthesia. The family history was negative; the pregnancy was uncomplicated; both parents were in their early twenties. At birth the infant had asphyxia pallida, but reacted promptly to warm and cold tubbing, tracheal suction and injection of alpha-lobelin. During the first four days of life the infant vomited blood and mucus. Pallor of the skin and mucous membranes developed; this apparent anemia was caused by the hemorrhagic diathesis of newborn.** Though the respiration had been somewhat labored since birth, severe tachy-dyspnea was not noted until the fourth day of life. On the fifth day of life, examination revealed crepitant rales over the lower and middle portions of both lungs. At this time a systolic murmur was heard all over the precordium. The clinical diagnosis of bilateral pneumonia was made. The condition of the child was considered critical; despite all therapy the infant expired on August 12, 1945 on the seventh day of life.

Autopsy.† Both lungs appeared edematous, mainly in the middle and lower lobes. Microscopically, bilateral basal confluent bronchopneumonia was demonstrated. The heart appeared greatly enlarged and globular, with a rounded apex. The right atrium appeared dilated; the venae cavae entered it in the normal fashion. The foramen ovale was open and almost 4 mm. in diameter; its membrane was loose (Figure 4). The tricuspid valve was morphologically normal but large (2 cm. in diameter). It led into a ventricle of unusually large dimensions. The volume of the chamber was grossly three-fourths of the entire volume of the heart. No interventricular septum was noted. The left atrium appeared normal in size and inner structure. The four pulmonary veins emptied into it as usual. The mitral ostium was very narrow (Figure 5), its diameter being 3-4 mm., and it was further narrowed by the vestige of the valvular leaflets. A rudimentary outlet pocket of 1-2 cc. capacity was situated in the anterior upper aspect of the common ventricle in the region normally occupied by the pulmonary

*Dr. Castrovinci saw this case in Gmunden, Austria in 1945 at the close of World War II.

**Unfortunately, the circumstances connected with the hectic events in the period and place where the infant was born did not allow routine laboratory tests, in order therefore to definitely evaluate the grade and type of the anemia noted on physical examination.

†Performed by Dr. H. Heinrichs.

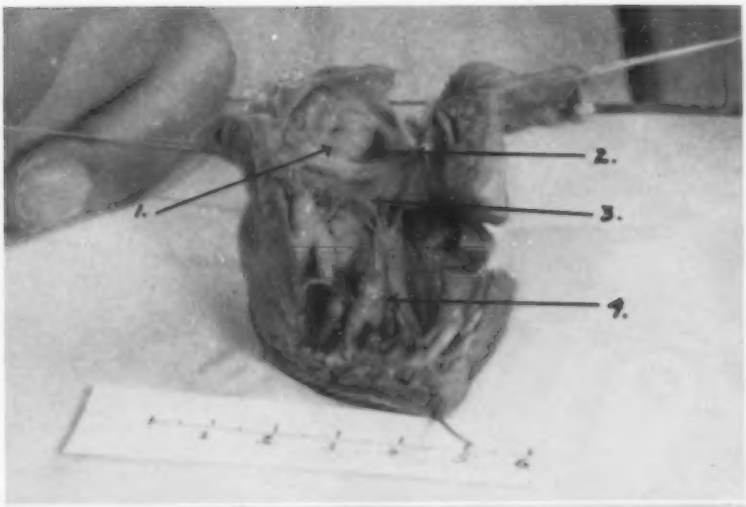

Fig. 4

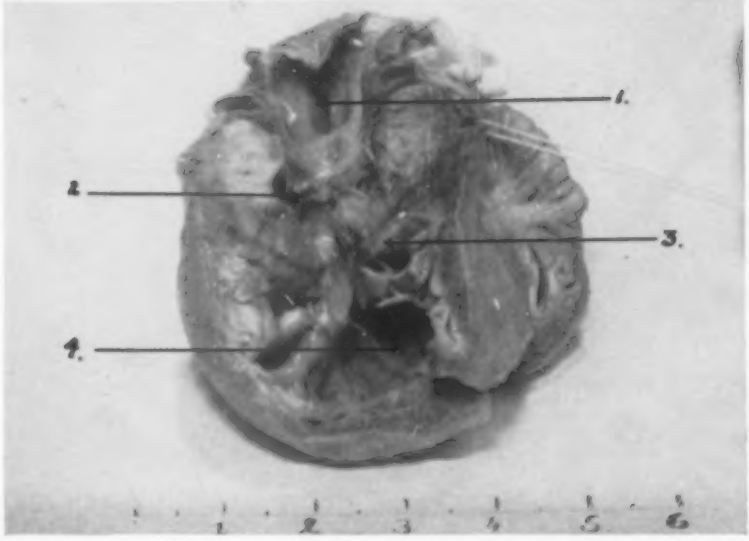

Fig. 5

Figure 4 (Case 2): View of the heart from the right, showing the dilated right atrium (1) a probe through the foramen ovale (2) the large tricuspid valve (3) and the single ventricle (4).—*Figure 5* (Case 2). The heart viewed from the left. Left atrium (1); hypolastic mitral ostium (2); muscular ridge (3) separating the outlet pocket from the single ventricle; single ventricle (4).

conus. The pocket was partially separated from the common ventricle by a muscular ridge (Figure 6). No vessel seemed at first to depart from it, but a scar was noted in its upper left corner. The pulmonary artery left the common ventricle at the right, and on a plane somewhat posterior to the outlet chamber; this artery appeared greatly enlarged (1½ cm. in diameter). It followed its natural course and gave origin to the right and left pulmonary arteries as usual. From its bifurcation a large ductus took origin and met the aorta between the innominate and the left carotid (Figure 7). The aorta from this point onwards appeared normal in size and orientation, but its ascending tract, as far as the innominate, was very narrow (1 mm.) and it lay anteriorly and slightly to the right of the pulmonary artery. The hypoplastic aorta was rooted to the wall of the rudimentary outlet chamber. The scar previously noted at the roof of such a chamber represented therefore an agenesic aortic orifice. The coronary arteries arose from the hypoplastic aorta in the normal fashion. The remainder of the autopsy was negative.

Anatomical diagnosis. 1) Trilocular biatrial heart with rudimentary outlet chamber and transposition of great vessels (type 1,A). 2) Atresia of the aortic orifice and severe hypoplasia of the ascending aorta (with patent ductus arteriosus). 3) Hypoplasia of the mitral valve, with wide foramen ovale. 4) Bilateral pneumonitis.

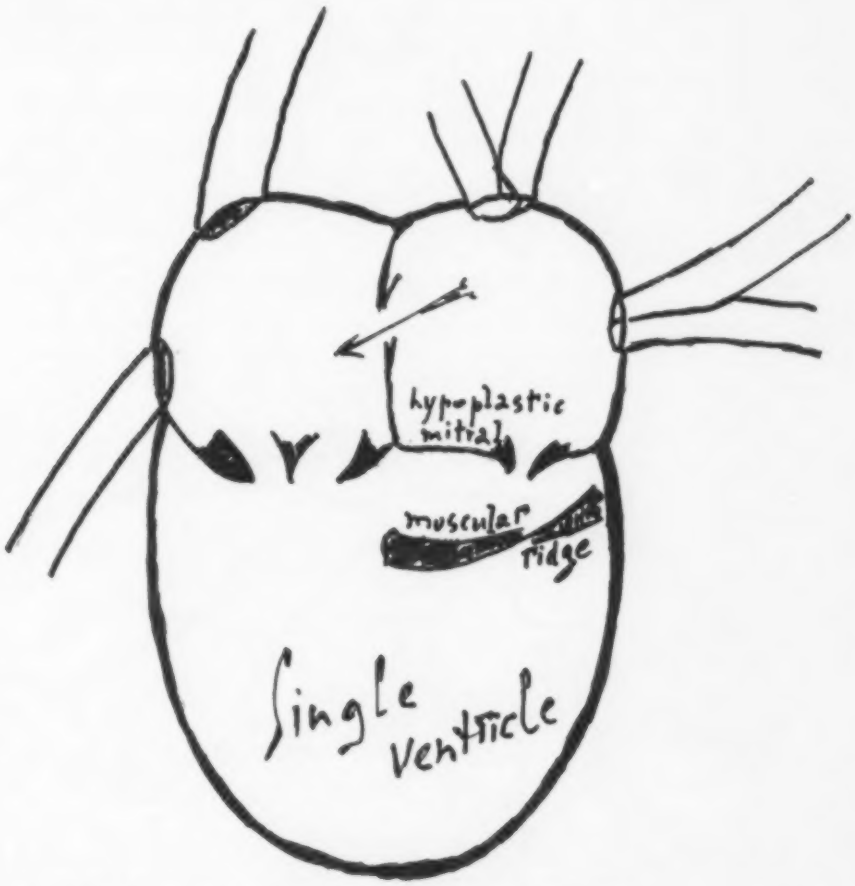

FIGURE 6 (Case 2): Diagram showing the three-chambered heart, the hypoplastic mitral orifice and the muscular ridge which delimited the outlet pocket.

Discussion

A) *Embryology.* The basic developmental error was essentially the same for both cases, namely an uneven partitioning of the truncus arteriosus. Up to the fourth week of embryonic life the heart consists of a single atrium and a single ventricle which continues in a single vessel: the truncus arteriosus. Towards the fifth embryonic week the subdivision of the truncus arteriosus into the aorta and the pulmonary artery is observed; the partitioning begins distally between the fourth and sixth aortic arches and progresses towards the heart. Into the lumen of the truncus two elongated ridges of connective tissue grow from the dorsal and the ventral surfaces, until they fuse in the middle of the lumen, thereby subdividing the truncus into two equal sized vessels, the aorta and the pulmonary artery. Simultaneously to the process of septation a complicated rotation of the two newly-formed vessels occurs. In the two cases under discussion the truncus ridges arose off center, asymmetrically, so that when they met two vessels of unequal dimensions were formed, a larger one: pulmonary artery, and another smaller: aorta (Fig. 8).

In the normal development of the heart the anterior aspect of the distal portion of the primitive ventricle bulges forward and swings to the right to form the bulbus cordis. During the septation of the ventricle, the bulbus is subdivided into a subaortic channel and the pulmonary conus. In the C.T.B.-a. the bulbus persists as the outlet chamber of the single ventricle and according to Rogers and Edwards[8] may constitute: a) a narrow subaortic; or b) a narrow subpulmonary, or c) a stenotic subaortic and

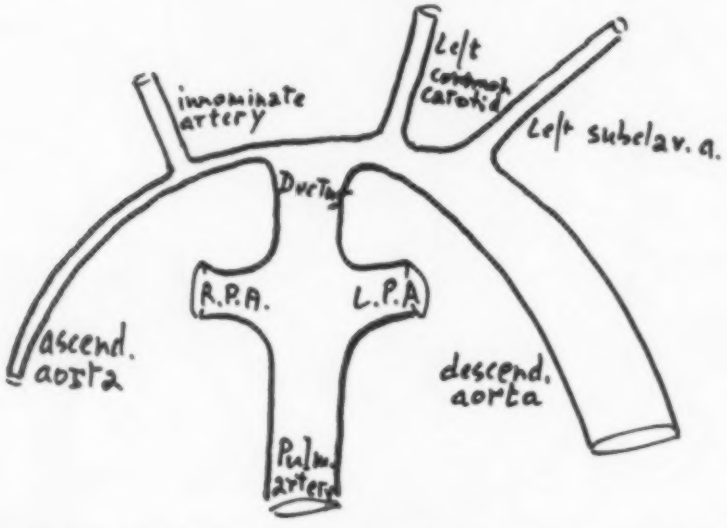

FIGURE 7 (Case 2): Diagram showing the hypoplastic ascending aorta, the pulmonary artery and the ductus arteriosus.

a stenotic subpulmonary channel, or d) a large outflow tract common to both great vessels. If the spiraling process of septation of the truncus and the rotation of the resulting great vessels is prematurely interrupted, an abnormal topographical relationship between the arteries and the outflow tract will result. In both our cases the rotation stopped at such a degree that the aorta happened to be at the level of the bulbus which had been subdivided into a stenotic subaortic channel and a large pulmonary outflow tract. The final result was that the great vessels were transposed, and the aorta took origin from a stenotic outlet.

As far as transposition of the great vessels is concerned it should be mentioned that Abbott recognizes two types: the *complete* transposition when the aorta leaves from the right ventricle and the pulmonary artery from the left; and the *correct* transposition when although the great vessels arise each one from their natural chamber, the topographical relationship between them is inverted, the aorta being anterior to the pulmonary artery. Actually this classification is not very useful in cases of C.T.B.-a. In such instances only the single ventricle is present and the only criterion in diagnosing a transposition is the relationship of either great vessel to the outlet chamber and the consequent reciprocal orientation of the great vessels. If the pulmonary artery arises anywhere but from the outlet chamber and it is located posteriorly to the aorta, a transposition exists which may be of various extent in different cases, depending on the degree of the embryonic arrest, but which may not be distinguished into a complete or correct type.

Normally the septum which divides the truncus progresses into the ventricular cavity to form the membranaceous portion of the interventricular septum (Fig. 9). The development of the interventricular septum occurs in two stages: first, the muscular part appears at the apex of the ventricle and grows up toward the base without reaching it; and then the membranaceous part descends from the truncus and encounters the primary muscular portion, thus completely separating the ventricular chambers.[10]

FIGURE 8: Diagrams showing the development of the ridges (1) into the lumen of the truncus arteriosus (2); normally (left and center diagram) the ridges grow until they fuse in the middle of the lumen (septum trunci). In the cases under discussion (diagram at the right) the ridges met off the center of the lumen, thus subdividing the truncus into two vessels of unequal caliber.

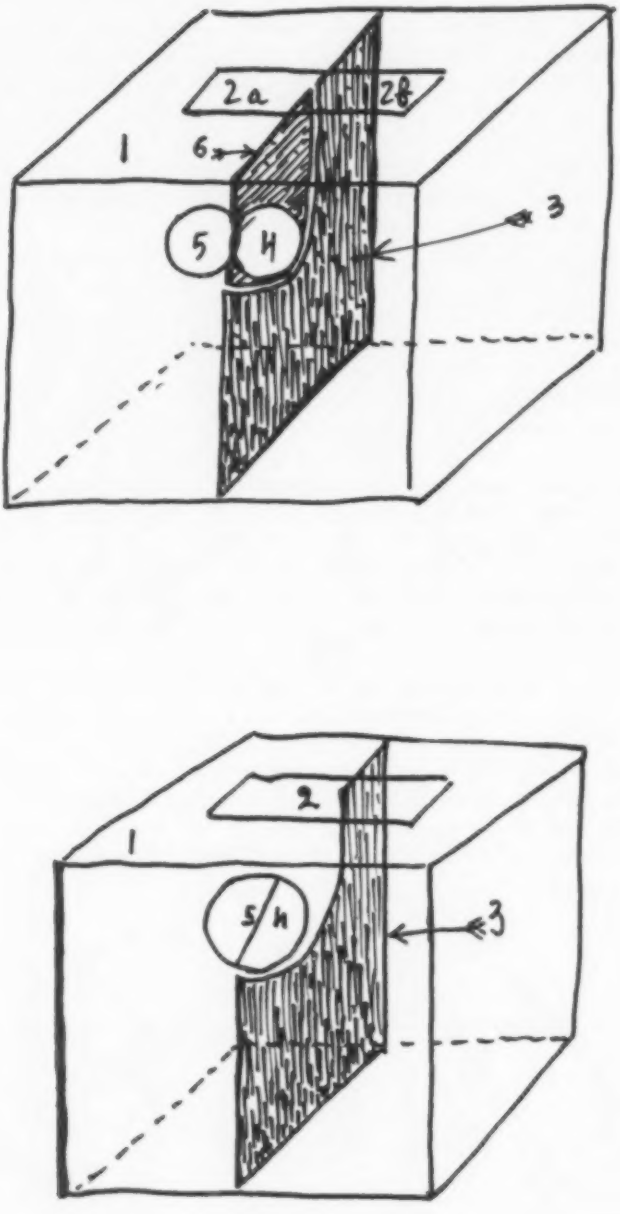

FIGURE 9: Diagrams showing the role of the septum trunci in completing the subdivision of the ventricles. 1) Ventricular cavity; (2) atrio-ventricular communis; 2a) tricuspid orifice; 2b) mitral orifice; 3) muscular portion of the interventricular septum; 4) aorta; 5) pulmonary a. 6) membranous portion of the interventricular septum which represents the progression of the septum trunci into the ventricular cavity. (Diagrams modified after Minissale, 26).

In the event of abnormal subdivision of the truncus, a defect of the interventricular septum quite often coexists, as in both our cases. It is presumed that in our cases a developmental error occurred between the fourth and sixth week of embryonic life, which caused not only the asymmetric growth of the truncus ridges, but also the failure of the muscular septum to develop at the apex of the ventricle.

Atresia or hypoplasia of the mitral orifice is a common feature in cases of C.T.B.-a., especially if atresia or hypoplasia of either great vessel coexists.

The atrio-ventricular orifices are formed by the subdivision and subsequent evolution of the endocardial cushions of the atrio-ventricular canal. The evolution of such endocardial cushions is closely related to the process of septation of the heart. In fact they favor the merging of both the interatrial septum with the interventricular and the latter one with the septum trunci.[11] Moenkeberg[12] attributed congenital mitral atresia to an abnormal position of either the interatrial or the interventricular septum or both. McIntosh[13] stressed the role of the interventricular septum, while Manhoff and Howe[14] attributed it to an overgrowth of the endocardial cushions. Brockman[9] explains his case of mitral atresia as due to excessive shifting of the atrial canal to the right, through failure of the upper portion of the bulbus to become incorporated into the right portion of the atrio-ventricular wall, so that the septum primum approaching the canal came to lie over the mitral region preventing the opening of the valvular orifice. It is quite likely that each of the above theories is correct, and that mitral atresia may be due to any one of the above mechanisms in particular instances. We, however, prefer to explain the concomitant mitral abnormality in both our cases without involving either the atrial septation or a primitive disturbance in the evolution of the endocardial cushions, or the shifting of the atrial canal, but rather blaming a single error as solely responsible for all the complex malformations of the two hearts under discussion. We have seen above that the septum trunci normally reaches the endocardial cushions and fuses with them contributing to their evolution into tricuspid and mitral valves. It is evident, therefore, that when the septation of the truncus and of the common ventricle is disturbed, the atrio-ventricular orifices secondarily will be affected. According to the degree of the rotation which has already occurred at the moment the septation of the truncus is completed and according to the side mainly affected by the uneven partitioning process, the result will be a common ventricle with atresia or hypoplasia of either the mitral or the tricuspid orifice. Our two cases represent two different degrees of an identical pathogenetic mechanism.

The premature closure of the foramen ovale in our first case might be explained in three different ways, relying on the different states of embryonic development. The foramen ovale is the opening enclosed by the septum secundum, once this has completed its pincer-like growth (Fig. 10). At its left the septum primum constitutes the valvula foraminis ovali. At the cephalic part of the septum primum the ostium secundum

represents the outlet of the foramen ovale. Generally the two septa fuse within the second year of life. In our case one of the following possibilities had occurred:

a) the ostium secundum did not develop in the septum primum, as Edwards and DuShane[15] thought probable in a similar case of theirs;

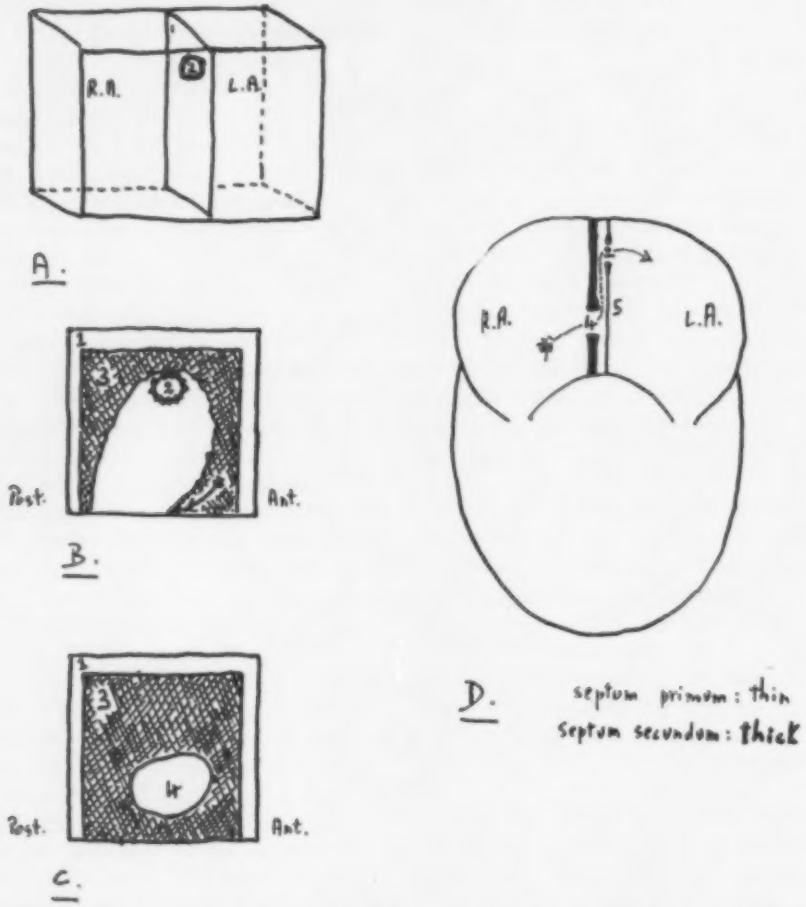

FIGURE 10: Diagrams showing the development of the foramen ovale and its valvula. A) Right and left atria with septum primum (1) and its ostium secundum (2). B) View from the right of the interatrial septum primum (1) with its ostium secundum (2) and of the developing septum secundum (3). The arrow shows the direction in which the anterior limb of septum secundum is growing across the atrial floor. C) View from the right of the complete septum secundum (3) and its foramen ovale (4). If the septum secundum overgrows no foramen ovale will result. D) Anterior view of a normal heart with a patent foramen ovale (4) and its valvular flap (5) represented by the remnant of the septum primum. Blood may flow from right to left entering the foramen ovale and emerging from the ostium secundum (2). If the two septa fuse completely, the foramen ovale is sealed and blood cannot flow from the right into the left atrium.

b) the septum secundum had overgrown so that the foramen ovale did not result;

c) the valvular flap might have been responsible for the closure, sealing itself against the septum secundum.

A last anatomical peculiarity has to be analyzed, before discussing the physio-pathological aspects of the malformations. In Case 1 there were only two pulmonary veins, one from each lung, entering the left atrium. The development of the pulmonary venous drainage follows a definite pattern. Up to the 5th week of embryonic life only one pulmonary vein enters the atrium; this vein is formed by a peripheral converging of smaller vessels. From each lung bud a small vein departs and conflowing with some similar ones, gives origin to a larger vessel, which in turn merges with others, until finally two pulmonary veins from each lung are formed. These two veins also converge into one, and the latter meets the homologue of the opposite lung to form the main pulmonary vein which opens into the left atrium. Between the 5th and the 8th week by a process of differential growth, the main pulmonary vein is absorbed into the dorsal atrial wall. Therefore, the two tributaries of the absorbed main vein, one from each lung, will open directly into the left atrium. The process of absorption continues up to the 11th week, when the latter two veins will also have been incorporated into the atrial wall, with the result that the usual normal feature of four pulmonary veins opening into the atrium is attained. In our case the process of gradual absorption of the pulmonary vessels into the atrial wall had been interrupted during an intermediate stage, and that resulted in only two pulmonary veins reaching the left atrium, instead of four.

B) *Pathologic physiology*. It is interesting to try to trace the course of circulation in our two cases. The venous blood coming from the cavae entered the right atrium and passed into the common ventricle. The ventricle expelled the blood wholly into the pulmonary artery since the aorta was of no practical use proximal to the ductus arteriosus. The blood then went partly to the lungs in the normal way and partly entered the descending aorta through the ductus. In the first case the return of oxygenated blood from the lungs to the heart was not feasible through the pulmonary veins since the secluded left atrium could not pour it either into the ventricle (mitral atresia) or into the right atrium (premature closure of foramen ovale). We must therefore suppose that oxygenated blood returned to the right atrium from the bronchial veins via the cava, as Lam, Knights, and Ziegler[16] presumed in a similar case of mitral atresia with a closed foramen ovale. In fact Bing,[17] Kroop,[18] et al. have shown clinically and experimentally that a vast capillary anastomosis can and often does exist between the bronchial veins and the pulmonary circulation in particular congenital cardiac malformations. This hypothesis seems the most likely one since although the autopsy failed to show any definite pathway, it ruled out the presence of anomalous vessels which could drain the blood either from the pulmonary veins into the ductus

venosus or the portal vein (as found by Edwards and DuShane[15]) or from the left atrium to the superior vena cava (Edwards and DuShane,[15] McIntosh[13]). Borow and Di Maio[19] reported a case similar to our first one in which the left atrium was completely isolated from the rest of the heart. They also were unable to objectively explain the venous return from the lungs. From the functional standpoint, cases of C.T.B.-a. associated with mitral atresia are biloculate as Barry and Isaac[2] pointed out. Our own case was all the more so since the mitral atresia was associated with premature sealing of the foramen ovale.

In our second case the venous return of blood from the lungs occurred normally via the four pulmonary veins, but owing to the hypoplasia of the mitral orifice only a small, functionally insignificant, quantity could enter the ventricle through it. Most of the blood passed from the left auricle to the right through the wide foramen ovale and from there into the single ventricle which expelled it into the pulmonary artery, whence, through the patent ductus, part of the blood finally reached the systemic circulation. Borow and Di Maio[19] state that all cases of mitral atresia reported in the literature had an interatrial communication except their own and the two above mentioned of Edwards and DuShane[15] and McIntosh.[13] To these we have to add Lam, Knights and Ziegler's,[16] discussed above, and our first one. In both our cases, therefore, the descending aorta received a mixture of venous and oxygenated blood. The mixing of the two bloods was conspicuous, occurring not only in the common ventricle but also proximally to it in right atrium and, in the first case, in the cavae. It would be expected that cyanosis is a compulsory feature. Actually it was not so in our second case. Apart from the fact that anaemia, complicating our second case, might by itself have prevented cyanosis from becoming manifest, another and more important factor must be taken into account. The presence and the degree of cyanosis in C.T.B.-a. is dependent not only on the admixture of oxygenated with unoxygenated blood, but above all on the position and the size of the great vessels in the single ventricle. Brown[20] stated that when a normal or dilated pulmonary artery is transposed, cyanosis if present is mild, whereas it tends to be severe if the pulmonary artery arises from the outlet chamber and/or is stenotic. Taussig[6] points out that presence or absence of cyanosis in C.T.B.-a. depends upon the volume of blood which reaches the lungs for aeration, that is, upon the size and position of the pulmonary artery. When this artery is of small caliber only a small quantity of blood may be aerated, and therefore a small volume of oxygenated blood mingles with a large quantity of venous blood, the result being an intense cyanosis. But if the pulmonary artery is of normal size and it is transposed so that the volume of blood which reaches the lungs is greater than that which flows into the systemic circulation, a large quantity of oxygenated blood will mix with a small volume of venous blood and visible cyanosis usually is absent or if present is minimal.

SUMMARY

Two cases of cor triloculare biatriatum are reported. The first case was complicated by mitral atresia, premature closure of the foramen ovale, and aortic hypoplasia. This was a case of a functionally biloculate heart. The infant died 16 hours after birth.

The second case concerns an infant who died at seven days of age. The main malformation was complicated by defects almost similar to those of the first case, namely: mitral hypoplasia, atresia of the aortic orifice and hypoplasia of the ascending aorta.

The great vessels were transposed in both cases (type 1,A of Rogers and Edwards).

The literature on the subject has been reviewed and an embryological discussion of the abnormality noted in the two hearts follows. The embryopathogenesis of these complex malformations is thought to be due to a primary faulty partitioning of the truncus arteriosus.

RESUMEN

Se relatan dos casos de corazón trilocular biatrial. El primero fué una complicación de atresia mitral, cierre prematuro de foramen oval e hipoplasia aórtica.

Este fué el caso de un corazón funcionalmente biloculado. El niño murió 16 horas después de nacido.

El segundo caso es de un niño que murió a los siete días de nacido. La principal malformación se complicaba por defectos casi similares a los del primer caso o sea: hipoplasia mitral, atresia del orificio aórtico, e hipoplasia de la aorta ascendente.

Las grandes vasos tenían transposición en ambos casos (tipo 1,A de Rogers y Edwards).

Se ha revisado la literatura al respecto y se hizo una discusión embriológica de la anormalidad notada en los dos corazones. La embriopatogenia de estas malformaciones congénitas se piensa debida a una defectuosa separación del tronco arterioso.

ZUSAMMENFASSUNG

Bericht über 2 Fälle von cor triloculare biatriatum. Der erste Fall war kompliziert durch eine Mitral-Atresie, vorzeitigen Schluss des Foramen Ovale und Hypoplasie der Aorta. Es war dies ein Fall eines funktionell biloculären Herzens. Das Kind starb 16 Studen nach der Geburt.

Der zweite Fall betrifft ein Kind, das im Alter von 7 Tagen starb. Die Hauptmissbildung war kompliziert durch ganz ähnliche Fehler wie die des ersten Falles, nämlich mitrale Hypoplasie, Atresie des Arificiums der Aorta und Hypoplasie der aufsteigenden Aorta.

Die grossen Gefässe waren in beiden Fällen transponiert (Typ 1,A von Rogers und Arwards).

Die Literatur über den Gegenstand wird einer Durchsicht unterzogen und eine Diskussion in embryologischer Hinsicht angeschlossen über die

an den beiden Herzen festgestellten Abnormalitäten. Es wird angenommen, dass die embryonale Pathogenese dieser komplexen Missbildungen die Folge einer primär falschen Teilung des truncus arteriosus ist.

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The Syndrome of Gastroduodenal Disease Associated with Chronic Cor Pulmonale *

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Manifestations due to malfunction of an organ which is no part of the primarily diseased system are often found in clinical medicine. Involvement of the gastroduodenal tract in chronic pulmonary emphysema with right heart disease, however, has not been fully recognized in spite of the fact that it occurs frequently. The lack of recognition of this syndrome is apparently because of its strange clinical behavior. The usual pattern of pain—food—relief is almost non-existent in these cases. Patients with this syndrome do not complain that pain awakens them from sleep in the early morning. They deny using milk or soda and seasonal relapses. Not only were hypertrophic gastritis and small peptic ulcers of the upper gastrointestinal tract silent, but even large multiple and penetrating ulcers have escaped detection because of the patients' freedom from typical pain.

This study was initiated by the following event. In November, 1954, a 64-year-old man was admitted to the Veterans Administration Hospital, Whipple, with the diagnosis of pulmonary emphysema and decompensated cor pulmonale. Symptoms of typical ulcer pain were not obtained. He died on the fifth night of hospitalization and at autopsy bleeding ulcers were found. He had been hospitalized on numerous occasions at several hospitals between 1949 - 1954, and from the records he had not complained of epigastric pain, and his gastrointestinal tract had never been investigated. Since then all patients suffering from chronic pulmonary emphysema and cor pulmonale have been subjected to x-ray studies of the gastroduodenal tract and, when necessary, gastroscopic examinations have been performed.

Material

This Veterans Administration Hospital serves as a center for chronic lung diseases. Patients afflicted with bronchial asthma and pulmonary emphysema have been attracted to this hospital from all parts of the country. They predominantly represent the group of intrinsic bronchial asthma. Other characteristics of this group are negative family and past history of atopy, and negative skin reactions, as well as unsuccessful response to antiatopic therapy.[1] Most of them have emphysema and bronchial infection or asthma. Only those cases of this group who developed right heart involvement were selected for studies of the gastroduodenal tract.

Excluded from this study were cases giving a history of bronchogenic carcinoma or metastatic lesions to the lung from other organs, specific infections, granulomatous or cystic diseases involving lung tissue leading to emphysema and cor pulmonale. Hypertension of the lesser circulation

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and right ventricular hypertrophy or dilatation caused by primary cardiac disease like mitral stenosis or left to right shunts were also excluded.

The diagnosis of chronic cor pulmonale was based upon the evidence of right ventricular hypertrophy clinically, roentgenologically or by electrocardiograms, and the exclusion of primary heart disease. On post mortem examination the finding of right ventricular hypertrophy or dilatation with the thickness of the right ventricle more than 5 mm. was diagnosed as cor pulmonale.[2]

The Veterans Administration Hospital, Whipple, has for many years maintained a 99% ratio of post mortem examinations which adds value to the results reported in this paper.

Findings

There were 65 cases of pulmonary emphysema and chronic cor pulmonale among 414 autopsies performed between January, 1948, and October, 1955. All were men with an average age of 56 years. Twenty-seven cases, out of the 65, revealed gastroduodenal disease. Ten had gastric and 11 had duodenal ulcers, while six had hypertrophic gastritis. The gastric ulcers were found mostly in the posterior wall of the lesser curvature close to the prepyloric region. Seven out of 27 cases with gastroduodenal disease died from massive hemorrhage, and two from hemorrhage and perforation. Five out of nine cases who bled massively were diagnosed several days before expiration. In only three of the entire group of 27, was a diagnosis established and treatment for ulcer instituted a long time antemortem.

A comparison was made of the above autopsy protocols with findings of patients on the medical wards and domiciliary members who had pulmonary emphysema and cor pulmonale. Sixty-five cases of this latter group were studied. They were subjected to x-ray studies of the gastroduodenal tract. Seven had gastric and 10 had duodenal ulcers, while five revealed both gastric and duodenal ulcers. The gastric ulcers were mainly in the prepyloric region of the lesser curvature. None were seen along the greater curvature of the stomach. There was marked prominence of the mucosal folds in the patients with ulcer as well as those with gastritis. Twenty-eight cases showed minimal to marked hypertrophic gastritis. Of the latter group, 13 were gastroscoped and in nine of them hypertrophic gastritis was seen.

Very striking is the fact that only 14 out of the group of 65 clinical cases had negative radiologic findings. Of the 51 who had positive findings on x-ray, only a few warranted such studies on the basis of the clinical picture.

These findings denote that the incidence of peptic ulcer is about thirty per cent, and if hypertrophic gastritis is added, the occurrence of gastroduodenal disease in this group of cases appears to be high. In the normal population the incidence of peptic ulcer is from 4 to 10 per cent.[3,4]

Case Reports

Case 1: G. E., 53 year old man was admitted to the Veterans Administration Hospital on October 4, 1949 because of progressive dyspnea and cough due to an upper respiratory infection. He had been a hospital patient on about six occasions during the past three years. He received periodic pneumoperitoneum which had improved his breathing. He first was aware of pulmonary disease in 1942, and in 1946 came to Arizona for climatic relief.

Examination revealed a chronically ill, poorly nourished white man with moderate dyspnea. The chest was emphysematous with diminished respiratory excursions. The lungs were hyperresonant throughout. Diminished tactile fremitus and decreased intensity of breath sounds were elicited. No areas of consolidation were noted. The heart sounds were distant. The blood pressure was 112/90 mm. Hg. The abdomen was tympanitic due to pneumoperitoneum. Remainder of examination was negative except for chronic sinusitis and deviated nasal septum.

An x-ray film of the chest revealed advanced emphysema and marked prominence of pulmonary arteries. An electrocardiogram was consistent with right heart strain.

He was treated with antibiotics, but took a downhill course manifested by increase in dyspnea, cyanosis, hepatomegaly and leg edema. Digitalis, oxygen, and mercurials were of no avail and he died on November 8, 1949.

At autopsy the right ventricle was 10 mm. thick. The trabeculae cornae in the right ventricle were large and projected into the cavity of the ventricle. The left ventricle was of normal thickness, 15 mm. The pulmonary vessels showed a moderate degree of atheromatous change. The right lung weight was 600 gm., and the left 1500 gm.

FIGURE 1

They were markedly congested and the left lower lobe was almost solid with edema. The air vesicles on the cut surface were increased in size and there were numerous bullae along the borders and at the apex. The bronchi contained a frothy red fluid. There was passive congestion of the liver, spleen and kidneys. In the gastrointestinal tract there was an ulcer approximately 1.5 cm. in diameter on the lesser curvature of the stomach, 2 cm. from the pylorus. This had a dark red base. On the anterior wall of the pylorus there was a stellate scar representing a healed ulcer and on the serosal surface there was radial fibrosis corresponding to the base of the ulcer. The remainder of the gastrointestinal tract was normal.

This case demonstrates that in spite of several hospitalizations over a three year period, no suspicion of peptic ulceration was entertained because of lack of symptoms.

Case 2: SH. H. H., this 54 year old white man was admitted on December 27, 1952. He had been hospitalized here on numerous occasions for treatment of pulmonary emphysema and bronchitis. His last admission was in March of 1952 at which time he had a spontaneous left pneumothorax. For approximately two weeks before his last hospitalization there had been progressive increase in dyspnea and a cough productive of thick yellow sputum. There was shortness of breath at rest.

On admission the physical examination revealed a well developed, poorly nourished white man who appeared chronically and acutely ill and dyspneic at rest. There was marked increase in the AP diameter of the chest, and respiratory excursions were labored, rapid and shallow. The lungs were hyperresonant. The breath sounds were distant and wheezing was noted over both lung fields. The heart tones were distant and rate was rapid. The blood pressure was 145/95 mm. Hg. The remainder of physical examination was negative.

Hospital Course: He improved somewhat on antiasthmatic medication and penicillin but remained quite short of breath. On February 2nd he developed right lower lobe pneumonia followed by evidence of cardiac failure with considerable edema and cyanosis. The pneumonia responded fairly well to penicillin. He then developed an episode of paroxysmal auricular tachycardia, which was controlled by quinidine. He continued to do poorly and had an episode of circulatory collapse marked by coldness and cyanosis of the extremities. The blood pressure dropped to imperceptible levels. The electrocardiogram showed increasing evidence of right heart strain. He died in March, 1953.

Autopsy: Both lungs were markedly voluminous with bullae over the upper and lower lobes. There was right lower lobe pneumonitis and the bronchial tree was filled with a thick exudate. The right ventricle measured 9 mm. There was dilatation of of the right auricle and ventricle. The trabeculae cornae and the papillary muscles of the right ventricle were hypertrophied. The pulmonary vessels showed a marked degree of sclerosis. On opening the stomach there was a large indurated ulcer which had perforated completely through the stomach and was walled off in the pancreas. The ulcer measured 3 x 1.5 cm., and was located on the lesser curvature of the stomach. The remainder of the gastrointestinal tract appeared normal.

Case 3: M. R. J., 60 year old white man, was admitted September 10, 1949. He was hospitalized previously on numerous occasions. On examination he revealed advanced emphysema and symptoms and signs compatible with decompensated cor pulmonale.

X-ray films showed marked emphysema, cardiac enlargement, and prominence of pulmonary branches. The electrocardiogram showed right ventricular hypertrophy. The hemogram and urinalysis were normal.

He was treated with digitalis, mercurial diuretics, low salt diet and bed rest with fairly good response. Within a period of one week, he developed a marked anemia which was discovered perchance by serial blood counts. Questioning at this time disclosed that he had gastric distress which was attributed to aminophyllin. X-ray films disclosed an ulcer on the lesser curvature with a 40 per cent retention in six hours. He finally died from a massive hemorrhage secondary to gastric ulcer.

On postmortem examination the heart weighed 480 gms. The right ventricle was 8 mm. thick. The stomach contained coffee ground material and dark brown fluid. On the lesser curvature, at the distance of 6 cm. from the juncture of the esophagus, there was an ulcer measuring 3.5 x 4.5 cms. A vessel containing a grayish-red thrombus projected into the base of the ulcer. The base of the ulcer was thin, and it had perforated. The small and large intestine appeared normal.

Case 4: M. W. A., 67 year old white man, was admitted on November 7, 1954. He developed recurrent upper respiratory infections 15 years previously complicated by emphysema and bronchial asthma several years thereafter. During a period of four years before this hospitalization he was hospitalized five times, each time for about three to seven weeks, at another hospital.

The physical examination showed a well developed, rather obese man, who appeared acutely and chronically ill. The chest was emphysematous. Respiratory excursions were shallow and labored. Wheezing sounds and rhonchi were heard throughout both lung fields. The heart sounds were distant. P-2 greater than A-2. The liver was felt

2 finger-breadths below right costal margin and was tender. There was 2 plus ankle edema. The blood pressure 120/70.

Laboratory: There was 2 plus albuminuria. The hemogram was normal. The sedimentation rate was 4 mm. The fasting urea was 39 mgm. per cent. The blood glucose was 120 mgm. per cent. The serum chlorides were 100 meq. and sodium 144 meq. X-ray films showed considerable emphysema of both lungs. Both pulmonary arteries appeared quite large, and there was sclerosis and aneurysmal dilatation of the left pulmonary artery. The heart was enlarged.

He was treated with digitalis, oxygen, mercurials, aminophyllin and antibiotic medication. He died suddenly on the 5th night of hospitalization.

The postmortem examination disclosed chronic pulmonary emphysema with passive hyperemia of posterior portions of both lungs. There was marked dilatation of the right side of the heart. The right ventricle measured 8 mm., and the right auricle was hypertrophied and dilated. The heart weight was 750 gms. The stomach contained liquid blood which extended through the duodenum, and the first three feet of the small intestine. The mucosa was hyperemic. In the first portion of the duodenum there were four ulcers, one measuring 1.5 x 1 cm. in diameter at a distance of 3 cm. from the pyloric ring on the lesser curvature. A small bleeding vessel was found at the base of this ulcer, and the base of the ulcer was covered by a grayish necrotic material. The other three ulcers were on the posterior wall. They measured approximately 1 cm. in diameter, and penetrated into the muscle. No adhesions were present on the serosal surface. The remainder of the gastrointestinal tract was lined throughout by a pale, smooth, glistening mucosa.

He underwent numerous hospitalizations, and the records disclose that at no time did he offer peptic ulcer symptoms. The absence of polycythemia in the face of chronic advanced emphysema and cor pulmonale could have possibly, as in cases two and three, made one suspicious of blood loss in this case.

Case 5: O. H. G., 57 year old white man, was admitted on March 11, 1955. He was well up until his 51st year of age when, following pneumonia, he continued coughing up green-yellowish sputum. In 1952, following an accident where he sustained fractures to four ribs, his pulmonary condition got progressively worse. He noticed dyspnea, wheezing, and chest pain on exertion; and in 1954 he was able to walk less than one block. He was then told for the first time that he had heart trouble. He denied any history of allergy or of digestive disturbances. He smoked about 10 cigarettes daily.

The physical examination showed a well developed and well nourished white man who appeared chronically ill. The chest was emphysematous. Respiratory excursions were shallow and labored. A few wheezing sounds were elicited throughout both lung fields. The heart sounds were distant. There was sinus tachycardia. Maximal apical pulsation was elicited in the subxiphoid region.

FIGURE 2A

FIGURE 2B

Laboratory: The white blood cell count was 9750 per cu. mm., neutrophils 71 per cent, lymphocytes 19 per cent, monocytes 8 per cent, eosinophils 1 per cent, basophils 1; 3 band cells. The red blood cells appeared normal. The hematocrit was 46 per cent. The sedimentation rate was 15 mm. (Cutler). The urinalysis was normal.

X-ray film of the chest showed considerable emphysema of both lungs, and there was heavy fibrosis adjacent to the left hilum. The pulmonary arteries were prominent. The heart was narrow and elongated. The electrocardiogram was consistent with right ventricular hypertrophy.

Hospital course: The sputum was cultured and since the organisms were sensitive to terramycin, the patient was treated with this. He was also treated for chronic sinusitis. When his dyspnea and wheezing appeared more severe and the tachycardia increased, he was subjected to a salt low diet, broncho-dilators and digitalis. A gastrointestinal series was performed and showed considerable coarsening of the gastric mucosa compatible with hypertrophic gastritis. The duodenal bulb showed irregularity in outline, and there was a small ulcer crater on the posterior wall (Fig. 1). The visualized loops of the small bowel appeared normal and there was more gastric retention at two hours than ordinarily seen. Gallbladder series were reported as normal. Gastroscopic examination done in April, 1955, revealed a cobblestone appearance in the lower third of the stomach. In the antrum there were several knob-like elevations of hypertrophic gastritis. The amount withdrawn during gastric analysis was 10, 10, 10 and 4 cc. The total acidity was 40, 92, 106 and 115 units. There were 20, 75, 80 and 90 units of free hydrochloric acid. Stool for occult blood was positive. Repeated hematocrits averaged 46 per cent. The eosinophil count was 198 per cubic millimeter. Liver function tests were normal. Urinary 17-ketosteroids were 10.7 mg. in 24 hours.

In addition to the above medications this patient was also put on a bland diet with milk and jello between meals, and methscopolamine bromide (pamine) and acetazoleamide (diamox) medication.

Gastroscopic examination repeated in November, 1955, six months after institution of treatment, showed considerable improvement over the previous examination. Only slight residue of hypertrophic gastritis was noted this time.

Case 6: M. O. R., 62 year old white man, entered the hospital September 2, 1955, compiaining of severe episodes of wheezing, coughing and dyspnea. His lung difficulty began in 1918, when he had the flu. However, it was not until 1941 that he noticed some shortness of breath on exertion and occasional wheezing. In 1950 an allergist performed numerous scratch tests and the patient was told that no specific reactions could be detected. He had been treated with injections of aminophyllin; and in 1952 was put on oral cortisone for three months. In 1953 he underwent several hospitalizations in Illinois where, in addition to cortef given for severe asthmatic attacks, he was treated with epinephrin and aminophyllin injections and phlebotomy. In 1954 he was treated with digitalis, diuretics, antibiotics and phlebotomies at a hospital in Arizona.

At the Veterans Administration Hospital, the following diagnoses were made: asthma, bronchial, intrinsic; polycythemia, secondary to pulmonary emphysema; decompensated cor pulmonale. The electrocardiogram showed P-pulmonale and right bundle branch block. Examination of the upper gastrointestinal tract showed the presence of a penetrating duodenal ulcer. There was a crater at the base on the lesser curvature of the bulb, which was about 5 mm. in size. The bulb was moderately deformed and the mucosal folds were swollen. There was no abnormality in the stomach, and no delay in gastric emptying. Additional laboratory findings were: white blood cell count 8750, neutrophils 60, lymphocytes 24, monocytes 8, eosinophils 1, basophils 1, band cells 6. Hematocrit 52 per cent. Urinalysis normal. The fasting urea nitrogen was 23 mgm. per cent. The serum sodium was 142 meq., the chlorides 101 meq., potassium 5.15 meq., and Carbon dioxide 30.5 meq. Stools had occult blood. Glucose tolerance test: fasting 120, one-half hour 178, one hour 200, two hours 140, three hours 115 mgm. per cent. All urine specimens negative for sugar. Gastric analysis: total acidity 48, 33, 40, 52, 81 units. Free hydrochloric acid: 0, 19, 29, 40, 59 units. The eosinophil count 185 per cubic millimeter. Vital capacity 2.1, maximum breathing capacity 33.7 liters per minute, or 40 and 30 per cent of normal respectively.

This patient required no more blood lettings during his last hospitalization. Steroid medication probably accelerated the peptic ulceration in this patient. Because of slow blood loss from his ulcer, as evidenced by occult blood in his stools, he had no recurrence of polycythemia in spite of progressing hypoxia.

Case 7: B. E. L., a 60 year old white man was admitted on July 7, 1955, because of marked respiratory distress. He stated that he was well up until eight years ago when he developed recurrent sinus infections associated with bronchial disease which ultimately was complicated by asthma. He had been subjected to a whole gamut of known medications for bronchial asthma, such as iodides, ephedrine, aminophyllin, as well as frequent antibiotic therapy. It was in 1948 when he was first given digitalis only for a short time and about one year prior to his present hospitalization he again

was given digitalis which he had been taking since. At no time did he notice leg edema. He offered no complaints referable to the gastrointestinal tract.

The physical examination revealed the patient to be markedly dyspneic, orthopneic, with marked cyanosis of lips and fingers. The chest was emphysematous with widening of intercostal spaces and increase in AP diameter. Wheezing sounds and rhonchi were elicited throughout both lung fields. Moist rales were heard at the left lower lung field posteriorly. The heart sounds were distant. There was sinus tachycardia. The maximal apical pulsation was in the subxiphoid region. Slight tenderness to pressure was present in the right hypochondrium. The prostate was moderately enlarged, and tender. The blood pressure was 120/80.

Chest x-ray film revealed emphysema (Fig. 2A). The electrocardiogram was consistent with cor pulmonale. Vital capacity 2.4 (normal 4.2). The maximum breathing capacity was 19.2 liters (normal 91.6 LPM).

X-ray examination of the stomach and duodenum disclosed marked coarsening of the gastric mucosa compatible with hypertrophic gastritis (Fig. 2B). Gastroscopic examination showed hypertrophied rugae in the body of the stomach. Other laboratory tests showed the following: white blood cell count 6000, neutrophils 69, lymphocytes 29, stabs two. Urinalysis normal. The serology was negative. Total protein 6.3, albumin 4.3 and globulin 2.0 gms. Stools for occult blood 10 times negative. Eosinophils 143 per cubic millimeter. Glucose tolerance test: fasting 87, one-half hour 151, one hour 162, two hours 132, three hours 80 mgm. per cent. All urine specimens negative. Gastric analysis not performed as he could not cooperate. Seventeen-ketosteroid excretion was 8.6 mgm. in 24 hours. Hematocrit 60 to 69, hemoglobin 19, red blood cells 7,000,000.

Patient has been treated with blood lettings about every two to three weeks. In

FIGURE 3

addition to routine bronchodilators, he has been on acetazoleamide (diamox), methscopolamine bromide (pamine) and a dietary regime for gastritis.

Case 8: F. M. F., 55 year old white man, came from Michigan to Arizona, on July 5, 1955, complaining of progressive exertional dyspnea with occasional chest pain. He has had chronic cough productive of mucoid sputum for the past several years. However, it was not until two years ago that he first experienced wheezing, shortness of breath, and recurrent peripheral edema. Although appetite has been good, he has lost approximately 10 lbs. during the three months prior to hospitalization. There were no gastrointestinal complaints. He smoked about 15 cigarettes daily.

The physical examination revealed marked emphysema. The apical beat was visible in midepigastrium, and there was one plus pitting edema of both lower legs and feet.

Chest X-rays showed both lungs had heavy markings throughout, and there was some scattered peribronchial infiltration at both bases. The heart appeared slightly enlarged, and there was prominence of both pulmonary arteries. Both leaves of the diaphragm were flattened. The electrocardiogram showed peaked P in leads 2, 3 and AVF, and tall S in V-4 and 5.

Examination of the gastrointestinal tract (Fig. 3) showed a markedly deformed prepyloric segment along with a markedly deformed duodenal bulb. In the duodenum the mucosal folds were swollen and there was a suggestion of a tiny ulcer crater on the posterior wall. In the prepyloric segment the lesser curvature was shortened, and somewhat irregular. Also on the lesser curvature of the antrum there was a persistent projection about 1 cm. in diameter and 0.5 cm. deep. This appearance suggested that there was a definite duodenal ulcer and a probable prepyloric and also a probable ulcer of the lesser curvature of the gastric antrum. There was no delay in gastric emptying.

Additional laboratory tests: white blood cell count 7300, neutrophils 68, lymphocytes 30, monocytes 1, eosinophils 1. Serology negative. Fasting urea nitrogen 9.7. Fasting glucose 87 mgm. per cent. Carbon dioxide 28.8 meq. Total protein 5.3, albumin 3.6, globulin 1.7 gms. Glucose tolerance: fasting 80, one-half hour 156, one hour 193, two hours 140, three hours 69 mgm. per cent. All urine specimens negative. Stools negative for occult blood. Gastric analysis: amount withdrawn: 10, 10, 10, 10 cc., total acidity: 83, 77, 88, 94, 87, free hydrochloric acid: 71, 62, 72, 79, 72. Hemoglobin 21.1, hematocrit 67, red blood cell count 6,700,000. Vital capacity and maximum breathing capacity 33 and 30 per cent of normal.

In addition to conventional medication and blood lettings, a bland diet and pamine were added to the therapeutic armamentarium.

All the last three cases have shown eosinopenia, hyperchlorhydria, and highest elevation of blood sugar one hour instead of normally one-half hour after ingestion of glucose while performing a glucose tolerance test.

Diagnosis

Usually, it is on the basis of the symptoms that a diagnosis of gastroduodenal disease is first suspected. In chronic cor pulmonale, classic symptoms of peptic ulcer or gastritis are characteristically missing. One is therefore forced to search for signs that would help establish a proper diagnosis.

A significant finding in some cases seems to be absence of polycythemia, due to slow blood loss in the stools. A normal hemogram in a state of marked hypoxia may serve as a diagnostic pointer. However, this could only be relied upon when other causes for chronic blood loss, or for bone marrow suppression, were excluded. In addition, many cases maintain their polycythemia because they do not bleed.

Anorexia, nausea and heartburn which frequently occur, are mostly ascribed to a variety of medications ingested by these patients.

For early and accurate diagnosis the ideal procedure would be to perform x-ray studies in all patients of this group. If further confirmation is required, gastroscopic examination should be performed as well.

Comment

A review of the medical literature discloses that the more frequent occurrence of pulmonary emphysema in cases of gastric ulcer was described

by Martii Hirvonen in Finland in 1951.[5] In 1952 two Canadian observers[6] reported the incidence of chronic ulceration to be 19 per cent in emphysema cases, and only 6.4% in the rest of 700 consecutive autopsies analysed. Lately, two authors[7] in this country reported the coexistence of chronic pulmonary emphysema in more than 40 per cent of cases of benign gastric ulcer, while the incidence of chronic pulmonary disease among the rest of their hospital was only 10 per cent. These observations seem to principally corroborate the independent results as presented in this paper.

It appears that all factors incriminated in the pathogenesis of peptic ulcer tend to play an exaggerated role as etiologic agents in gastroduodenal disease associated with pulmonary emphysema and chronic cor pulmonale. We have been able to demonstrate in almost all of our clinical cases the presence of high free and total acid in the stomach. The high values are certainly interesting, especially in our gastric ulcer patients which are otherwise known to be mostly associated with normal values.[4,11] No periarteritis or necrotizing arteritis could be demonstrated on microscopic studies of the tissues involved. Contrary to the popular belief, we have also been unable to elicit signs of eosinophilia on repeated blood smears. Eosinopenia has rather been an almost constant finding. This in association with findings of persistent highest elevation of blood sugar one hour, instead of normally one-half hour, after glucose intake on a fasting stomach may point to increased adrenal cortical activity in these patients. Adrenalin, to which these patients are subjected frequently, also effects increased corticosteroid output via hypothalmic pituitary-adrenal cortex stimulation. Cortisone and corticotropin have been shown to cause an increase in both acid and pepsin secretion of the stomach.[8] Also because of their protein catabolic action and prevention of fibroplasia, their adverse effect upon the gastroduodenal mucosa cannot be questioned.

Another mechanism contributing to gastroduodenal disease in chronic pulmonary emphysema with right heart disease could possibly be carbonic anhydrase.[9] Hypercapnia causes an increased production of carbonic acid by carbonic anhydrase in the parietal cells, which leads to hyperchlorhydria.

Among other mechanisms histamine deserves special mention. Histamine was shown to be liberated in increased amounts not only during attacks of atopic but also of nonatopic bronchial asthma. It does not necessarily depend upon antigen-antibody interaction for its release. Cell damage, due to various causes such as infection or anoxemia, is associated with increased histamine concentration. Histamine causes increased gastroduodenal smooth muscle contraction just as it causes bronchospasm. In addition, it causes marked gastric secretion and hyperchlorhydria.[10]

The occurrence of death from hemorrhage at the site of peptic ulceration is because of the absence of a peptic ulcer history to suggest the proper diagnosis. The fact that these patients belong to an older age group with more progressive arteriosclerotic changes also favors a fatal outcome when bleeding occurs.

The most intriguing phenomenon in these cases, however, is the lack of typical peptic ulcer pain and a history of intermittency and periodicity.

No definite explanation can be offered for this manifestation.

It may be postulated that the higher brain centers are insensitive to distress impulses originating in the upper gastrointestinal tract because of preoccupation with continuous abnormal stimuli transmitted from the broncho-pulmonary tree. However, it was definitely observed that these same patients, when concurrently afflicted with other painful maladies, do complain of pain no less than other patients suffering from a similar condition and free from pulmonary embarrassment. The problem is still more puzzling in the face of marked hyper-acidity found to exist in these cases.[11]

The results of gastric secretory, radiographic and gastroscopic studies following therapeutic measures will be reported in a subsequent paper.

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SUMMARY AND CONCLUSIONS

1. The syndrome of gastroduodenal disease associated with pulmonary emphysema and chronic cor pulmonale is described. Of 65 cases of pulmonary emphysema with right heart disease on whom postmortem examinations were performed, 21 revealed peptic ulcer of the stomach and duodenum, and six showed hypertrophic gastritis. A like number of clinical cases studied with x-rays of the upper gastrointestinal tract yielded a 30 per cent ratio of peptic ulcers and a high incidence of gastritis. Almost all of these cases, with a few exceptions, did not have the history or pain typical of peptic ulcer. A high proportion of these cases died from hemorrhage and perforation.

2. In the absence of characteristic symptoms, lack of polycythemia in a state of marked hypoxia might occasionally serve as a diagnostic pointer for peptic ulcer or bleeding gastritis. Absence of polycythemia, however, may also be due to other causes. In addition, many of these cases do not bleed and maintain the polycythemia.

3. It is advised that all patients of this group be subjected to x-ray studies, and if necessary gastroscopic examinations of the gastroduodenal tract. This is the only means of establishing a proper diagnosis and instituting early treatment in order to forestall serious complications.

RESUMEN Y CONCLUSIONES

1. Se describe el síndrome gastroduodenal asociado al enfisema pulmonar y al corazón pulmonar crónico. De 65 casos de enfisema pulmonar con enfermedad del corazón derecho en quienes se hizo autopsias, 21 tenían úlcera péptica del estómago y del duodeno, y seis tenían gastritis hipertrófica. Un número semejante de casos clínicos estudiados a los rayos X del tracto gastrointestinal alto, demostraron un 30 por ciento de úlceras pépticas y una elevado frecuencia de gastritis. Casi todos los casos con

pocas excepciones carecían de antecedentes de dolor típico de la úlcera crónica. Una elevada proporción de estos casos fallecieron de hemorragia y de perforación.

2. En ausencia de síntomas característicos, la falta de policitemia en un estado de acentuada hipoxia podría ocasionalmente dar un indicio de úlcera péptica o de gastritis sangrante. La ausencia de policitemia sin embargo, puede deberse a otras causas. Además muchos de estos casos no sangran y mantienen una policitemia.

3. Se aconseja que todos los enfermos de este grupo se sometan a estudios a los rayos X y que si es necesario se las hagan gastrocopías. Este es el único modo de establecer un diagnóstico correcto y de instituir un tratamiento temprano para evitar serias complicaciones.

RESUME

1. L'auteur décrit un syndrome dans lequel s'unissent une affection gastro-duodénale, un emphysème pulmonaire et un coeur pulmonaire chronique. Sur les 65 cas d'emphysème pulmonaire associé á une atteinte du coeur droit, dont on fit l'examen post-mortem, 21 présentaient un ulcère de l'estomac et du duodénum, et six une gastrite hypertrophique. Un nombre égal de cas étudiés cliniquement avec examens radiologiques de l'appreil gastro-intestinal donna 30% d'ulcères et un nombre élevé de gastrites. La plupart de ces cas, à quelques exceptions près, n'avaient aucun antécédent ou douleur caractéristiques de l'ulcère. Dans une forte proportion, hémorragie et perforation entrainèrent la mort de ces malades.

2. En l'absence de cymptômes caractéristiques, le manque de polycythémie dans un état d'insuffisance respiratoire marquée pourrait éventuellement constituer un élément de diagnostic en faveur de l'ulcère ou de la gastrite hémorragique. Cependant l'absence de polycythémie peut avoir d'autres causes. Par ailleurs beaucoup de ces malades n'ont pas d'hémorragie et gardent leur polyglobulie.

3. L'auteur est d'avis que tous les malades de ce groupe devraient être soumis à des examens radiologiques de l'appareil digestif et si nécessaire à des examens gastroscopiques. C'est le seul moyen d'établir un diagnostic correct et d'instituer un traitement précoce susceptible de prévenir des complications graves.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

1. Beschreibung des Syndroms einer gastroduodenalen Erkrankung in Verbindung mit Lungenemphysem und chronischem cor pulmonale. In einer Gruppe von 65 Fällen von Lungenemphysem mit Erkrankung des rechten Herzens, bei denen postmortale Untersuchungen vorgenommen wurden, ergaben sich 21 peptische Geschwüre von Magen und Duodenum, und 6 litten an hypertropher Gastritis. Eine gleiche Zahl von klinischen Fällen, deren oberer Magendarmtrakt röntgenologisch untersucht worden war, lieferte ein Verhältnis von 30% von peptischen Geschwüren und ein hohes Auftreten von Gastritis. Fast alle diese Fälle hatten mit wenigen Ausnahmen keine Vorgeschichte von für ein peptisches Geschwür typischen

Schmerzen. Ein hoher Anteil dieser Fälle starb an Blutung und Perforation.

2. Bei Ausbleiben charakteristischer Symptome kann gelegentlich das Fehlen einer Polycythaemie bei einem Zustand ausgesprochener Hypoxie als ein diagnostischer Wink dienen für ein peptisches Geschwür oder eine Gastritis mit Blutung. Das Fehlen einer Polycythaemie kann jedoch auch auf andere Ursachen zurückzuführen sein. Ausserdem bluten viele dieser Fälle nicht und behalten ihre Polycythaemie.

3. Es wird empfohlen, alle Kranken dieser Gruppen röntgenologischen Untersuchungen zu unterziehen und, falls erforderlich, gastroskopischen Prüfungen des Magendarmkanals. Dies ist das einzige Mittel, zu einer richtigen Diagnose zu gelangen und eine Frühbehandlung einzuleiten, um schwereren Komplikationen vorzubeugen.

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Tuberculosis in Children and Adolescents

A Five to Fifteen Year Follow-up of 105 Patients

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Introduction

The following study was undertaken with the primary purpose of determining the course and fate of children admitted to the Pollak Hospital for Chest Diseases with a diagnosis of tuberculosis during the 10 years from January 1, 1939 to December 31, 1948 inclusive. The hospital was opened at its present site shortly before the former date. There were 110 admissions through the age of 15 years during this interval. This report is based on 105 (95.4 per cent) of the group in whom data was available at least five to 15 years after their first hospital admission. Almost 80 per cent were observed at intervals in the chest clinics of Hudson County. Information on others was obtained from private physicians or other hospitals. Clinic and public health nurses rendered valuable assistance in supplying some pertinent data. Evaluation on the follow-up status was recorded as of January 1, 1954. While the total number of patients reviewed is small, it is nevertheless felt that such a study is of value. It is recognized that the course and results of management of a chronic disease such as tuberculosis can be properly assessed only after a number of years. This is a longitudinal rather than a cross-sectional study with the findings reported after a minimum of five years observation or multiples of five following the first hospitalization. Second, with some exceptions, these patients did not receive anti-microbial therapy or when given was inadequate according to present concepts, and therefore might constitute a rather good control group for long range comparison with the chemotherapy and resected cases of more recent origin.

Epidemiological Data

All had positive tuberculin reactions and in 76 (72.3 per cent) there was a positive contact history of exposure to a known case of tuberculosis. Table I shows the distribution of patients as regards sex, race and age on the first admission. The average length of hospital stay per admission was 346 days.

Classification of Disease

The diagnoses of disease listed below is that made on the first hospital admission. The following classification of primary tuberculosis was used in the final review of patients.

Active—The parenchymal or glandular components or both is demonstrable on the chest x-ray film.

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TABLE I

		Number	Per Cent
Sex	Male	46	43.7
	Female	59	56.1
Race	White	74	70.4
	Colored	30	28.5
	Yellow	1	0.9
Age	Under 1 year	7	6.6
	1 - 5 years	27	25.7
	6 - 10 years	21	20.0
	11 - 15 years	50	47.5

(a) *simple*—the pulmonary component should be less than lobar in extent with no cavitation. The mediastinal nodes may be of any size. The lesion should be stationary or regressive on serial roentgenograms. Sputum or gastric cultures may be positive on rare occasions.

(b) *progressive*—this is an active case that shows evidence of progression or exceeds the criteria mentioned above on the first admission.

Healed—There should be complete resolution or stabilization with or without calcification of the previous lesions. Symptoms should be absent. If and when sputum or gastric cultures are done they should be negative.

A. *Primary Infection*—total 55 cases (52.3 per cent)

Active

(a) simple—28

(b) progressive—24:—this includes five with miliary tuberculosis and two additional cases who had miliary plus meningeal disease

(c) pleurisy with effusion—3

Thirty-eight per cent presented symptoms (elicited from child or parent) referable to the primary pulmonary or to extra-pulmonary involvement. Positive results on culture were obtained in the gastric washings of 44 (26.4 per cent) children in whom this was done on admission.

B. *Re-infection Pulmonary Tuberculosis (active)*—47 (44.8 per cent)

minimal—21 (includes one case with large associated pleural effusion)

moderately advanced—22

far advanced—4

C. *Cases with extra pulmonary lesions and without x-ray film evidence of primary or re-infection tuberculosis but with positive tuberculin test and confirmation by biopsy*—3

Tuberculosis of lymph nodes—2

Tuberculosis of skin—1

D. *Extrapulmonary tuberculous lesions (other than meningeal) associated with x-ray evidence of primary or re-infection tuberculosis* (some patients presented multiple lesions)

Superficial adenopathy—7
laryngitis—5
ileo-caecal—2
peritonitis—1
bone and joint involvement—11
sternum—1
elbow—1
ribs—1
hip—1
knee—1
skull—2
spine—4

Re-admissions

During the 15 years observation period (1939-1953 inclusive), there were 23 (22 per cent) who had more than one hospital admission. Among the 55 cases of primary infection, the re-admissions were four (7.4 per cent)—3 (5.4 per cent) because of subsequent development of re-infection pulmonary disease and one because of miliary plus meningeal dissemination. Re-admissions for the original re-infection group totaled 19 (40 per cent); 17 re-entered the hospital because of new pulmonary lesions or re-activation of the pre-existing foci; and three of them had new associated extra-pulmonary foci, one of whom died from meningitis. The reason for re-admission of the remaining two was for meningitis and one of these also had hematogenous miliary tuberculosis.

Therapy and Results

A. *Medical*

1. *Rest*—complete or partial was the basic therapy in all patients during hospitalization.
2. *Chemotherapy*
   (a) *For primary infection*: Two received streptomycin alone for three to four months because of progressive parenchymal infection with extrapulmonary lesions. Both showed considerable improvement and are alive with inactive disease. The eight in the primary infection group who had miliary and/or meningeal tuberculosis and died were observed in the pre-antibiotic period.
   (b) *Group C*: One child in Group C with cervical adenitis and a draining sinus was given streptomycin and promizole for three months together with local Kromayer lamp treatment. Under this therapy, the glands receded, the sinus closed and the patient is well.
   (c) *For re-infection tuberculosis*: There were a total of 13 who received drug therapy ranging from three days to seven months. While this chemotherapy was inadequate according

to present regimens, beneficial results were seen in some. Six received streptomycin alone, five for exacerbation of parenchymal disease and one for meningitis (died). Five had streptomycin and PAS and two isoniazid in addition, one of whom died three days after its use from meningitis.

3. *Artificial pneumothorax*—This procedure was attempted in 33 of the 47 re-infection cases and discontinued as ineffective in 15. In the group of 18 in whom effective pneumothoraces were obtained, 14 (66 per cent) have remained well four to 12 years after re-expansion; eight had unilateral and six bilateral collapse and four received a short course of chemotherapy in conjunction with pneumothorax. The remaining four had relapse of their disease two to three years after re-expansion (all of them with bilateral collapse); three obtained chemotherapy and in two, artificial pneumoperitoneum was employed also with good results. The fourth died at home 10 years after his first hospital admission. In other words, 17 (94 per cent) of the 18 original effective pneumothorax cases are living and well as of January 1954 as against eight (53 per cent) of the 15 cases in whom pneumothorax was unsuccessfully attempted or discontinued. There was only one case of empyema in the whole group.

B. *Surgical Measures*

1. *Phrenicectomy*—There were five patients who had this operation, one in combination with artificial pneumoperitoneum. This was the only case in whom an effective result was secured and the only surviving patient in this category.
2. *Extra-pleural pneumothorax*—The procedure was ineffective in the four on whom it was done and only two of them are still alive.
3. *Endocavitary drainage*—One who had a previous unsuccessful attempt at pneumothorax and phrenicectomy, had this operation which was also a failure. The patient died many months later.
4. *Thoracoplasty*—An effective surgical collapse was obtained in one after extra-pleural pneumothorax had failed. Subsequently he was re-admitted and died from meningitis seven years from the time of his first hospitalization. Another had decortication followed by thoracoplasty for tuberculous empyema incurred during pneumothorax therapy. This patient is living six years after operation.
5. *Resectional surgery*—A colored boy, age 14, who was re-admitted because of progressive disease had left upper lobectomy under coverage of chemotherapy. Spread of remaining disease gradually occurred and he died 27 months post-operatively.

Follow-up Status

The status of the 105 patients recorded below is that of January 1, 1954.

A. *Cases with primary infection*—total 55

1. *Living*—47 (85.4 per cent)
   (all are attending school, working or able to work)
   (a) at least 5 years after first hospital adm.—3 (6.3 per cent)
   (b) 6 to 10 years after first hospital adm.—30 (63.8 per cent)
   (c) 11 to 15 years after first hospital adm.—14 (29.9 per cent)
2. *Died*—8 (14.6 per cent)
   (a) in Pollak Hospital—6
   (b) in home or another hospital—2

B. *Cases with re-infection tuberculosis*—total 47

1. *Living*—32 (68 per cent)
   (a) inactive disease 30 (93.7 per cent)
   (attending school, working or able to work)
   active disease—2
   living at least 5 years from first hospital adm.—5
   living 6 to 10 years from first hospital adm.—20
   living 11 to 15 years from first hospital adm.—7
   (b) active disease—2 (living at least five years from first hospital admission)
2. *Died*—15 (32 per cent)
   (a) in Pollak Hospital—12
   (b) at home or another hospital—3

C. *Cases with extra-pulmonary lesions alone without chest x-ray evidence of primary or re-infection tuberculosis*—total 3

1. *Living*—3
   (attending school or working)
   (a) living 6 to 10 years after first hospital adm.—1
   (b) living 11 to 15 years after first hospital adm.—2

Analysis of Mortality Cases

A. *Among cases with primary infection*—eight deaths. Five were due to miliary tuberculosis and three to miliary plus meningeal disease. The length of survival varied from four to 78 days after admission. All of them were white children equally divided between the sexes; at the time of death, two were less than one year of age, two between one to two years, and four between seven to eight years. They were hospitalized before antibiotic therapy became available.

B. *Among cases with re-infection tuberculosis*—15 deaths. Twelve (80 per cent) died from progressive pulmonary tuberculosis; five of them had amyloidosis as a complication with or without associated extra-pulmonary lesions and five expired following large hemoptyses. The three remaining patients died of tuberculous meningitis two to seven years after their first hospitalization for parenchymal pulmonary disease which became inactive. Three of the 15 had minimal, 10 moderately advanced and two far advanced lesions on the initial admission. There were 10 white patients and nine females in the group of 15 and ages at death ranged from 12 to 24 years with an average of 17.7. The

length of survival from the time of the first admission to death extended from five to 120 months with an average of 60.2 months. Three patients lived for 10 years.

Comment

This study enhances one's respect for the potential dangers of the primary infection and more especially for re-infection tuberculosis in the adolescent. In the former, the review indicates that the most important single prognostic factor is the age at which the infection first appears. The younger the child, the greater the risk. Fifty per cent of the cases died at the age of two years or under. Prognosis is also less favorable in infants with the acute febrile form of the clinically established primary infection. Of less significance is the parenchymal distribution as seen on the x-ray film. This is in contrast to the re-infection type of the disease. At this point, it is important to emphasize the desirability, whenever possible, of taking upright films rather than supine or prone films in order to avoid the erroneous pitfall of mediastinal widening, interpreted as adenopathy; the mediastinal shadow is definitely exaggerated in the recumbent position. Atelectasis, segmental or lobar was diagnosed roentgenologically in about 9 per cent of the cases. Bronchoscopy or bronchography were not performed. The most important single criterion for discharge in many cases was roentgen stability of the primary lesion. Three (5.4 per cent) patients were re-admitted because of re-infection type of pulmonary tuberculosis. Analyzing the causes of death, it is pertinent to repeat that all of the eight patients (14.6 per cent) died from miliary and/or meningeal complications. These deaths occurred before the advent of anti-microbial drugs. The salvage of most, if not all, of this group could be anticipated with the current regimens of chemotherapy. Other extrapulmonary lymphatic or hematogenous metastatic lesions could well be minimized also by present day treatment.

In contrast to the primary infection group, as regards management and prognosis, are the patients who presented evidence of re-infection disease, 55 per cent of whom had advanced pulmonary tuberculosis on admission. The re-admission rate was 5½ times higher and the death rate more than twice as high than for the primary infection cases. The best results were obtained by the combination of rest and artificial pneumothorax. The latter procedure was attempted in 70 per cent of the cases and 94 per cent of the group who had an effective collapse are now living five to 15 years compared to 53 per cent who had unsuccessful or ineffective pneumothorax. Eighty per cent died from progressive pulmonary tuberculosis and the remainder from tuberculous meningitis. Again, significant reduction in the complications and mortality can be visualized with modern treatment.

SUMMARY

1. In the 10 year period between 1939 - 1948 inclusive, there were 110 admissions at the Pollak Hospital through the age of 15 years for tuberculosis. This study is based on 105 (95.4 per cent) patients in whom clini-

cal information was available five to 15 years after their first entrance into the hospital.

2. These cases are classified. Of the group of 55 (52.3 per cent of the total) with primary infection (parenchymal and/or glandular components), 47 (85.4 per cent) are alive and well five to 15 years later. The remainder (14.6 per cent) died from hematogenous complications (miliary and meningeal) in the pre-antibiotic era.

3. Of the group of 47 (44.8 per cent) with re-infection pulmonary disease, 32 (68 per cent) are living five to 15 years later (up to January 1, 1954) and all but two are inactive. Fifteen (32 per cent) in this group died; 12 from progressive pulmonary tuberculosis and three from tuberculous meningitis. The re-admission rate was 40 per cent compared to 7.4 per cent for the first infection cases.

4. The remaining three (all living) had extra pulmonary tuberculous foci without roentgen evidence of thoracic disease.

5. Prognostic factors in the primary infection and therapeutic measures in the re-infection groups are discussed. The best results in the latter patients were obtained with the use of bed rest and artificial pneumothorax.

RESUMEN

1. En los diez años transcurridos entre 1939 y 1948 hubo 110 entradas al Hospital Pollak más de los 15 años de edad. Este estudio se basa en 105 enfermos (95.4 por ciento) en los que pudo obtenerse información clínica de 5 a 15 años después de su primera entrada al hospital.

2. Estos casos se clasificaron. Del grupo de 55 (52.3 por ciento del total) con infección primaria (con componentes parenquimatosos y/o ganglionar), 47 (85.4 por ciento), están vivos y bien después de 15 años. Los demás (14.6 por ciento) murieron de complicaciones hematógenas (miliares y meninges) en la era pre-antibiótica.

3. Del grupo de 47 (44.8 por ciento) con tuberculosis de reinfección, 32 (68 por ciento) viven después de 5 a 15 años (Hasta Enero de 1954) y todos, menos dos, son inactivos. Quince (32 por ciento) de estre grupo murieron; 12 de tuberculosis pulmonar progresiva y tres de meningitis tuberculosa. La proporción de readmisiones fuó de 40 por ciento comparada con 7.4 por ciento para los casos de primoinfección.

4. Los restantes tres enfermos (todos vivos) tuvieron focos extrapulmonares de tuberculosis sin evidencia radiológica de enfermedad torácica.

5. Se discuten los factores pronósticos en la infección primaria y las medidas terapéuticas en el grupo de reinfección. Los mejores resultados en este último, fueron obtenidos por el reposo en cama y el neumotórax artificial.

RESUME

1. Dans la période de 10 ans qui s'étend de 1939 à 1949 il y eut 110 admissions pour tuberculose à l'Hôpital Pollak. Il s'agissait de malades âgés de plus de 15 ans. Le auteurs présentent une étude basée sur 105 malades (95,4%) chez lesquels ils purent obtenir des renseignements cliniques valables 5 à 15 ans après la première admission à l'Hôpital.

2. Ces cas se répartissent ainsi. Dans un groupe de 55 malades (52,3% du total) atteints de primo-infection (parenchymateuse et/ou ganglionnaire) 47 malades (85,4%) sont en vie et bien portants, 5 à 15 ans après. Les autres (14,6%) sont morts de complications hématogènes (miliaires et méningées) avant l'époque des antibiotiques.

3. Dans un groupe de 47 malades (44,8%) atteints de réinfection pulmonaire, 32 (68%) sont en vie 5 à 15 ans après (jusqu'au 1er janvier 1954) et tous sauf deux sont stabilisés. 15 malades de ce groupe (32%) sont morts: 12 de tuberculose pulmonaire évolutive, trois de méningite tuberculeuse. La proportion des ré-admissions a été de 40% alors que pour les primo-infections, elle a été de 7,4%.

4. Les trois autres malades (tous vivants) ont présenté des foyers tuberculeux extra-pulmonaires sans qu'on ait pu mettre radiologiquement en évidence chez eux une atteinte thoracique.

5. Les auteurs mettent en discussion les éléments de pronostic dans la primo-infection et les moyens thérapeutiques employés pour les cas de réinfection. Les meilleurs résultats chez ces derniers malades furent obtenus grâce au repos intégral et au pneumothorax artificiel.

ZUSAMMENFASSUNG

1. Während der 10-Jahres-Periode zwischen 1939 und 1948 einschliesslich erfolgten 110 Zugänge in das Pollak-Krankenhaus im Alter ab 15 Jahren wegen Tuberkulose. Diese Untersuchung geht von 105 Patienten aus (95,4%), für die 5-15 Jahre nach ihrer ersten Einweisung in das Krankenhaus klinische Daten zur Verfügung standen.

2. Diese Fälle werden in Gruppen eingeteilt. In der Gruppe der 55 (52,3% der Gesamtzahl) mit Primärinfektion (parenchymal und/oder glanduläre Komponente) sind 5-15 Jahre später 47 (85,4%) am Leben und wohlauf. Die übrigen (14,6%) starben infolge haematogener (miliarer und meningealer) Komplikationen in der prae-antibiotischen Aera.

3. In der Gruppe von 47 Fällen (44,8%) mit pulmonaler Reinfektionskrankheit sind 32 (68%) 5-15 Jahre später am Leben (bis 1.1.1954), und mit 2 Ausnahmen sind alle inaktiv. 15 (32%) in dieser Gruppe starben; 12 infolge fortschreitender Lungentuberkulose und 3 infolge tuberkulöser Meningitis. Die Ziffer für Wiedereinweisungen betrug 40% im Vergleich zu 7,4% bei den Fällen mit Erstinfektion.

4. Die übrigen 3 Kranken, alle am Leben, hatten extrapulmonale tuberkulöse Herde ohne röntgenologische Anzeichen thorakaler Erkrankung.

5. Besprechung prognostischer Faktoren für die Gruppe der Primärinfektion und therapeutischer Massnahmen für die Gruppe mit Reinfektion. Die besten Ergebnisse bei Kranken der letzten Gruppe wurden erzielt durch Bettruhe und künstlichen Pneumothorax.

The Degree of Relaxation Obtained in Different Diameters of the Lung By Pneumoperitoneum and Phrenic Paralysis, When Used Either Singly or in Combination*

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Introduction

This subject is presented under three main headings:

A. Effect on Apico-Basal Diameter of the Diseased Lung.

B. Effect on the Differential Vertical Relaxation of the Upper and the Lower Lobes.

C. Effect on the Transverse Diameter of the Base of the Lung.

A. The Effect of Pneumoperitoneum Compared with Pneumoperitoneum Combined with Phrenic Paralysis on the Apico-Basal Diameter of the Diseased Lung.

Banyai[1] (1946) reported on 40 patients. With pneumoperitoneum alone, the maximum elevation of the diaphragm on inspiration was 7.3 cm. on the right side and 6.4 cm. on the left side.

Thompson Evans[2] (1953) made a study of reduction of apico-basal diameter after pneumoperitoneum, and pneumoperitoneum plus phrenic crush.

TABLE I
HIS AVERAGE FIGURES WERE

Form of Collapse	Rise of Right Dome Cm.	Reduction of A. B. Diameter Per Cent	Rise of Left Dome Cm.	Reduction Per Cent
On pneumoperitoneum alone	5.7	25	5.3	22
Pneumoperitoneum plus right phrenic crush	8.6	36	4.7	17
Pneumoperitoneum plus left phrenic crush	4.0	18	7.6	30

In order to avoid errors due to variation in the size of the thorax a reliable estimate of vertical relaxation of the lung in a given individual can be made by finding out the percentage of reduction in the apico-basal diameter as suggested by Banyai. (It will be called "Vertical Relaxation

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Index" in the text hereafter). It is calculated easily by the following formula:

$$\text{Vertical Relaxation Index} = \frac{\text{Decrease in apico-basal diameter}}{\text{Original apico-basal diameter}} \times 100$$

$$\text{For example V.R.I.} = \frac{4 \text{ cm.}}{20 \text{ cm.}} \times 100 = 20$$

In other words there has been a reduction of 20 per cent in the apico-basal diameter of the lung in this case. It can also be expressed as vertical relaxation index being 20, in this case.

The apico-basal diameter is measured in centimeters from the highest point of the apex of the lung (the fixed point taken in these studies was the lower border of the transverse process of the first thoracic vertebra) to the highest point of the corresponding dome of the diaphragm.

I have made a study of vertical relaxation index of a group of 62 patients first on pneumoperitoneum alone, and later on the same patients when pneumoperitoneum was combined with phrenic paralysis. A total of about 280 roentgenograms were taken before and during treatment at the end of full inspiration from a distance of six feet, with the patient in the upright position about one to two hours before refills. A total of about 560 measurements were made. Apico-basal diameter was measured with a 30.5 cm. plastic transparent scale. Index of vertical relaxation was found after pneumoperitoneum alone and then compared with index of vertical relaxation (I.V.R.) after phrenic paralysis was added in those patients. That gave quite an accurate idea, as to how much additional relaxation of the lung one can expect after combining phrenic paralysis to an already existing pneumoperitoneum.

Patients were divided into two groups. Group "A" of 32 patients, received maximum of 1,000 cc. of air at seven to 10 days interval guided by fluoroscopy. Group "B" of 30 patients received a maximum of 600 cc. of air at weekly intervals.

TABLE II—GROUP "A"
AVERAGE INDEX (PERCENTAGE) OF VERTICAL RELAXATION OF THE DISEASED LUNG IN GROUP "A" PATIENTS

Group "A" Patients	Average Index of Vertical Relaxation		Average Increase in I.V.R. by Addition of Phrenic to P.P.*
	On P.P.* Alone	On P.P.* Plus Phrenic	
16 Males	17.9	29.03	64.0
16 Females	14.08	27.84	97.7
In the whole group "A"	16.0	28.5	78.1

*P.P. = Pneumoperitoneum.

It will be seen from this table that the addition of phrenic paralysis to established pneumoperitoneum in males increased the index of vertical relaxation by 64 per cent on the average. In the female, the addition of

phrenic paralysis to established pneumoperitoneum gave an average increase of 97.7 per cent in the "Index of Vertical Relaxation."

Taking the group "A" as a whole it may be concluded that on the average, the addition of phrenic paralysis to established pneumoperitoneum increases the rise of the paralysed diaphragm by about 78 per cent.

TABLE III—GROUP "B" PATIENTS

AVERAGE INDEX (PERCENTAGE) OF VERTICAL RELAXATION OF THE DISEASED LUNG IN GROUP "B" PATIENTS

Group "B" Patients	Average Index of Vertical Relaxation		Average Increase in I.V.R. by Addition of Phrenic to P.P.
	On P.P. Alone	On P.P. Plus Phrenic	
20 Males	10.3	22.4	117.4
10 Females	6.1	25.3	Not measured reasons given in text
In the whole group "B"	8.4	23.8	183.3

It will be seen from this table that in males addition of phrenic paralysis to pneumoperitoneum gave an average increase of 117.4 per cent in the Index of Vertical Relaxation. In females the average increase in the Index of Vertical Relaxation by addition of phrenic paralysis to pneumoperitoneum could not be calculated with any statistical justification; because out of seven patients in whom pneumoperitoneum was followed by phrenic paralysis, the amount of refills (about 500 cc. to 600 cc.) given were so small that x-ray films taken before instituting phrenic paralysis either showed only traces of air under the dome or no air at all.

TABLE IV

COMPARATIVE FIGURES OF INDEX OF VERTICAL RELAXATION OF THE TWO GROUPS

Group of Patients	Average Index of Vertical Relaxation	
	On Pneumoperitoneum Alone Per Cent	On Pneumoperitoneum Plus Phrenic Per Cent
Group "A"	16.0	28.5
Group "B"	8.4	23.8

It will be noticed that in group "A," whereas Index of Vertical Relaxation with pneumoperitoneum alone, is 90 per cent more than that in group "B", the index of Vertical Relaxation with Pneumoperitoneum plus phrenic paralysis is only about 20 per cent more than that in the "B" group.

It is apparent that when pneumoperitoneum is used as a sole collapse measure 600 cc. refills at weekly intervals do not give adequate rise of

diaphragm. But when pneumoperitoneum is combined with phrenic paralysis it is seen that even 600 cc. refills at weekly intervals give significant rise of the paralysed dome and insignificant rise of non paralysed dome. As a result of this phenomenon, there occurs a unilateral selective pneumoperitoneum with much smaller degree of visceroptosis. We have found that this is the collapse measure of choice in unilateral lower and mid zone disease.

The Reduction in Apico-Basal Diameter in Patients in Whom Phrenic Paralysis Preceded Pneumoperitoneum.—There were 11 patients in whom for one reason or the other phrenic paralysis was done before pneumoperitoneum. In such cases the first elevation of the diaphragm was solely due to phrenic paralysis.

Since significant difference was found in the right and left side figures, they were calculated separately and subjected to close scrutiny and analysis to arrive at the cause of such difference.

TABLE V

AVERAGE INDEX (PERCENTAGE) OF VERTICAL RELAXATION OF THE DISEASED LUNG ON PHRENIC ALONE FIRST AND LATER ON PHRENIC PLUS PNEUMOPERITONEUM IN BOTH GROUPS "A" AND "B"

In Both Group of Patients	Average Index of Vertical Relaxation		Average Increase in I.V.R. by Addition of P.P. to Phrenic
	On Phrenic Alone	On Phrenic Plus P.P.	
Left side	11.5	31.3	172.0
Right side	9.3	32.5	249.4

By phrenic paralysis alone on the left side the "Average Index of Vertical Relaxation" was 11.5 per cent and maximum was 23.3 per cent whereas on the right side the average was 9.3 per cent and maximum was 13.2 per cent.

When pneumoperitoneum was induced and established in such cases, it was found that it increased the "Index of Vertical Relaxation" by 172 per cent on the left side and 249.4 per cent on the right side.

An interesting fact which emerged from this study was, that the average index of vertical relaxation was greater with pneumoperitoneum alone (16 per cent usually equal on both sides unless atelectasis occurs) than with phrenic paralysis alone (9.3 per cent on the right side and 11.3 per cent on the left side). However when phrenic paralysis was later added to established pneumoperitoneum, the average index of Vertical Relaxation became 28.4 per cent. Similarly when pneumoperitoneum was later added to phrenic paralysis average Index of Vertical Relaxation became 31.9 per cent. This clearly shows that although the Index of Vertical Relaxation with phrenic operation alone was significantly less than with pneumoperitoneum alone, it increased ultimately to approximately the same degree when both operations were combined irrespective of the fact which precedes. If at all, the index of vertical relaxation is a little more when phrenic paralysis preceded pneumoperitoneum, probably by virtue of the

fact that longer period of paralysis leads to greater loss of tone of diaphragmatic musculature. Nevertheless, for other more important reasons, it is logical that pneumoperitoneum should precede phrenic paralysis by a few weeks. The advantage is that one can know whether diaphragm can rise adequately or is bound down by adhesions or whether there are extensive intraperitoneal adhesions causing persistent abdominal pain to warrant abondoning pneumoperitoneum.

B. The Effect of Pneumoperitoneum and Pneumoperitoneum Plus Phrenic on the Differential Vertical Relaxation of the Upper and the Lower Lobes.

The opinion is divided among some workers on this subject. Rilance and Warring,[3] Trimble[4] and Fowler,[5] obtained better results and greater incidence of closure of cavities situated in mid and lower zones than in upper zones. On the contrary Keers,[6] Anderson and Winn,[7] Crow and Welchel[8] after an analysis of their work feel that there is no significant difference in the healing response of any section of the lung with pneumoperitoneum or pneumoperitoneum plus phrenic paralysis. They further add that the nature of the lesion appears to be more important than its location in the lung from the point of view of its response to this form of collapse.

Thompson Evans[2] (1950) tried to measure the contraction of different lobes on the right side in a few cases where the transverse fissure was visible. He found that in the healthy right lung the relaxation induced by pneumoperitoneum was taken up 78 per cent by the mid and lower lobes and 22 per cent by the upper lobe. In a diseased lung the respective figures with pneumoperitoneum were 59 per cent and 41 per cent and with pneumoperitoneum plus phrenic paralysis 63 per cent and 37 per cent. The influence of the site of the lesion on this differential relaxation was not measured.

In this work an effort has been made to study the problem of differential relaxation in greater detail and to determine the influence of the site of the disease on the degree of relaxation which different lobes undergo with pneumoperitoneum and phrenic paralysis.

There is almost a consensus of opinion among most authorities that other factors being equal the therapeutic result of pneumoperitoneum or pneumoperitoneum plus phrenic are in direct proportion to the degree of rise of the diaphragm and the degree of vertical relaxation of the lung. In order to get some objective evidence, we decided to measure the "differential relaxation" of the upper lobe on the one hand, and of the lower and middle lobe on the other, in those cases where the transverse fissure was visible.

Observations and measurements were made in two cases where right lung was healthy, in eight cases of upper lobe lesions, in one of lower lobe lesions and in two where the entire right lung was diseased.

Measurements were taken on roentgenograms from apex to the mid point of the transverse fissure and then from the latter to the highest point of the dome. Roentgenograms were taken on the same fixed criteria as described earlier.

Results and Discussions

1. In the healthy right lung (Table VI) the vertical relaxation which occurs with pneumoperitoneum is taken up 66.5 per cent by the lower and middle lobes and 33.5 per cent by the upper lobe.

TABLE VI

DIFFERENTIAL RELAXATION IN UPPER AND LOWER LOBES OF RIGHT LUNG (WHEN RIGHT LUNG WAS HEALTHY)

Nature of Collapse Therapy	Number of Cases	Total Reduction in Apico-Basal Diameter	Reduction in Apex to Transverse Fissures Diameter	Index of Vertical Relaxation of Upper Lobe	Reduction in Transverse Fissure to Dome Diameter	Index of Vertical Relaxation of Lower & Middle Lobes
		Cm.	Cm.	Per Cent	Cm.	Per Cent
With P.P.* alone	1	2.3	1	43	1.3	57
	2	2.5	0.6	24	1.9	76
Average				33.5		66.5

P.P. = Pneumoperitoneum.

2. In the case of lower lobe disease with cavity (Table VII), the relaxation on pneumoperitoneum alone was 14.3 per cent in the upper lobe and 85.7 per cent in the lower and the middle lobe. When phrenic was added the respective figures were zero per cent and 100 per cent due to segmental atelectasis in the lower lobe.

TABLE VII

DIFFERENTIAL RELAXATION IN UPPER AND LOWER LOBES OF RIGHT LUNG (IN LOWER LOBE DISEASE WITH CAVITY)

	Total Reduction in Apico-Basal Diameter	Reduction in Apex to Transverse Fissures Diameters	Index of Vertical Relaxation of Upper Lobe	Reduction in Transverse Fissure to Dome Diameter	Index of Vertical Relaxation of Lower and Middle Lobes	REMARKS
	Cm.	Cm.	Per Cent	Cm.	Per Cent	
With P.P. alone	3.5	0.5	14.3	3	85.7	
With P.P. plus phrenic	5.5	0.0	0.0	5.5	100	Whole of the relaxation taken up by L.L. no manifest, gross atelectasis. Segmental atelectasis probable

3. Where the whole of the right lung was diseased (the lower lobe had bigger cavity) (Table VIII) the proportion of vertical relaxation with pneumoperitoneum plus phrenic was 73.7 per cent for lower and middle and 26.3 per cent for the upper lobe.

4. In cases with upper lobe disease with or without cavity, (Table IX) the proportion of vertical relaxation on pneumoperitoneum alone was 53.3 per cent in the upper and 46.7 per cent in the lower and middle lobes. In this series of six patients, there was one case in which due to massive atelectases of the upper lobe all the vertical relaxation (100 per cent) was taken up by it and proportion for lower and middle lobe was recorded as (0 per cent). If this case is excluded from the series the figure will be 44 per cent for the upper lobe and 56 per cent for lower and middle lobes.

TABLE VIII

IN DISEASE OF THE WHOLE OF THE RIGHT LUNG

	Number of Cases	Total Reduction in Apico-Basal Diameter	Reduction in Apex to Transverse Fissure Diameter	Index of Vertical Relaxation of Upper Lobe	Reduction in Transverse Fissure to Dome Diameter	Index of Vertical Relaxation of Lower & Middle Lobes	REMARKS
		Cm.	Cm.	Per Cent	Cm.	Per Cent	
With P.P. alone only 2 refills of 100 cc. and 150. cc.	1	0.0	0.0	0.0	0.0	0.0	Trace of air under the domes
With P.P. and phrenic one month after	1	5.0	1	20.0	4.0	80.0	
Five months after	2	5.8	1.5	26.3	4.3	73.7	With P.P. & phrenic well established

TABLE IX

DIFFERENTIAL RELAXATION IN THE UPPER AND LOWER LOBES OF RIGHT SIDE IN UPPER LOBE DISEASE

Nature of Collapse Therapy	Reduction in Apico-Basal Diameter	Reduction in Apex to Transverse Fissure Diameters	Index of Vertical Relaxation of Upper Lobe	Reduction in Transverse Fissure to Dome Diameters	Index of Vertical Relaxation of Lower & Middle Lobes
	Cm.	Cm.	Per Cent	Cm.	Per Cent
After P.P. alone average of 6 cases	2.4	1.4	53.3	1.01	46.7
After phrenic alone average of 2 cases	2.25	0.75	35	1.5	65
After P.P. plus phrenic average of 4 cases	5.16	2.16	41.2	3.0	56.6

With phrenic alone in upper lobe disease the relaxation is 35 per cent in upper lobe and 65 per cent in the lower and middle lobes.

In other words the vertical relaxation induced by pneumoperitoneum or pneumoperitoneum plus phrenic paralysis is chiefly taken up by the lower and middle lobes except when the upper lobe is predominantly diseased. Then the latter also takes up nearly half the vertical relaxation. In short the vertical relaxation induced is distributed between the various lobes, in this proportion.

1. In a healthy lung about two-thirds in the lower and middle and about one-third in the upper lobe.
2. In upper lobe disease, a little less than half in the lower and middle and a little more than half in the upper lobe.
3. In lower lobe disease about four-fifths in the lower and middle, and one-fifth in the upper lobe.
4. In disease of the whole of the right lung, the proportion will depend on, which lobe is more diseased and also which one undergoes segmental or lobar atelectasis.

C. The Effect of Mediastinal Shift and Compensatory Rib Movement on the Transverse Diameter of the Lower Lung Fields Following Pneumoperitoneum Combined with Phrenic Paralysis.

Fox[9] (1950) advanced a modified concept of the effect of pneumoperitoneum plus phrenic nerve paralysis on the transverse diameter of the lung base. He stated that the vertical relaxation induced by the combined precedure is to some extent off set by the broadening of the lung field at the base on the paralysed side, due to two factors:

1. Partly due to mediastinal shift away from the paralysed side.
2. Partly due to the increased compensatory movement of the lower ribs which follows the operation of phrenic paralysis.

Of these two factors, he studied the effect of mediastinal shift in 80 cases, and found that average reduction of the width of the opposite lower hemithorax due to mediastinal shift was 11.4 per cent. He has not mentioned the average increase in the transverse diameter of the base of the lung on the paralysed side, nor has he measured the increase in this transverse diameter due to compensatory rib movement.

Mediastinal Shift—The horizontal distance between the side of the vertebral bodies and the point of maximum bulge in the cardiac outline on the non-paralysed side was measured before the beginning and after the full establishment of treatment. The difference between these two distances was taken to be the measurement of mediastinal shift. Corrections were made in the measurements of mediastinal shift for any clavicular tilt present.

The Transverse Basal Diameter—The horizontal distance between the sides of the vertebral body and the inner margin of the periphery of the bony thorax was measured by a line passing through the highest point of the diaphragm before the beginning and after the full establishment of treatment. The point which needs emphasis is, that after the base of the

lung has been lifted up in the thorax by the rise of the paralysed diaphragm with pneumoperitoneum, the transverse diameter should now be taken at the level of the highest point of the diaphragmatic contour, and not at the original level of the diaphragm, for the base of the lung has moved up considerably in the thorax which is roughly cone-like. Our results were as follows:

TABLE X

Side	Reduction in Apico-Basal Diameter Per Cent	Increase in Basal Transverse Diameter		Total Increase in Basal Transverse Diameter
		Due to Mediastinal Shift Per Cent	Due to Rib Movement	
1. P.P. plus right phrenic crush, average of 8 cases	27.8	6.5	5 per cent in half the cases. But in the other half 5 per cent diminution occurred	11.5 per cent in half the cases. 1.5 per cent in the other half
2. P.P. plus left phrenic crush, average of 4 cases	23.8	2.5	2.2 per cent in ¼ the cases. But in the ¾ 1 per cent diminution occurred	5 per cent in ¼ the cases. 1.5 per cent in ¾ the cases

Results and Discussion

A. On the right side: (eight cases of pneumoperitoneum plus right phrenic crush were studied). The average reduction in apico-basal diameter was 27.8 per cent. The average increase, on the paralysed side, in the transverse diameter at the base of the lung due to mediastinal shift was 6.5 per cent, whereas the effects of compensatory rib movements increased the transverse diameter of the base by 5 per cent in half the cases. In the other half the transverse diameter at the base was diminished by 5 per cent, thereby showing that the effect of the lifting of lung base in the cone-like thorax diminished its transverse diameter more than the compensatory rib movements could increase it at that level.

Taking the effect of both mediastinal shift and compensatory rib movement together, we find that the transverse diameter of the lung base was increased by 11.5 per cent in half the cases and by 1.5 per cent in the other half.

B. On the left side: (four cases of pneumoperitoneum plus left phrenic crush were studied). The apico-basal diameter was diminished by 23.8 per cent and the transverse basal diameter was increased by 2.5 per cent due to mediastinal shift. Compensatory movements increased the transverse diameter in one-quarter of the cases only by 2.25 per cent. The combined effect of mediastinal shift and the compensatory rib movement was to increase the basal transverse diameter in one-quarter of the cases by 5 per cent and in the remaining three-fourths cases by 1.5 per cent. We are aware the number of the cases studied with left side treatment

was only four and, therefore, too small for statistical analysis.

This small increase in transverse diameter was only present in those cases where the mediastinum was mobile and further that it did not materially neutralize or offset the benefits resulting from reduction of apico-basal diameter.

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SUMMARY

1. A comparative study of the reduction in apico-basal diameter has been made on 62 patients, first on pneumoperitoneum alone, and later on the same patients when pneumoperitoneum was combined with phrenic crush.

2. In "group A" of 32 patients who received 1000 cc. of air at seven to 10 day intervals, the average reduction in apico-basal diameter was 16 per cent with pneumoperitoneum alone, and 28.5 per cent after addition of phrenic crush; that is, phrenic crush caused a further increase in vertical relaxation by about 78 per cent.

3. In "group B" of 30 patients who received a maximum of 600 cc. of air at weekly intervals, the average reduction in apico-basal diameter was 8.4 per cent with pneumoperitoneum alone, and 23.8 per cent after addition of phrenic crush.

4. When pneumoperitoneum was used as a sole collapse measure, 600 cc. refills at weekly intervals did not give adequate rise of the diaphragm. When phrenic crush was added, it was seen that even 600 cc. refills at weekly intervals gave adequate rise of paralysed dome, and either no rise or insignificant rise of non-paralysed dome.

5. In eleven patients, phrenic paralysis on one side was performed first and pneumoperitoneum was added later. It was noticed that with phrenic paralysis alone on the left side, the average reduction in apico-basal diameter was 11.5 per cent and maximum was 23.3 per cent. Whereas on the right side, the average reduction was 9.3 per cent and maximum was 13.2 per cent. With the addition of pneumoperitoneum the average reduction was 31.3 per cent on left side and 32.5 per cent on the right side.

6. The vertical relaxation induced by pneumoperitoneum or pneumoperitoneum plus phrenic paralysis is distributed between different lobes, in different proportions depending on the site of the major lesions.

7. Pneumoperitoneum combined with phrenic paralysis slightly increases the transverse diameter of the base of the lung due to the shift of a mobile mediastinum and compensatory rib movements. This insignificant increase in transverse basal diameter was only present in those cases where the mediastinum was mobile and it did not materially neutralize or offset the benefits resulting from reduction in apico-basal diameter.

RESUMEN

1. Un estudio comparativo de la reducción del diámetro apico-basal se ha hecho en 62 enfermos, primero con neumoperitoneo solo y después en el caso de los enfermos con neumoperitoneo combinado con frenopraxis.

2. En el grupo "A" de 32 enfermos a quienes se insulfaron 1000 cc. cada siete a diez días, la reducción del diámetro apicobasal por término medio fué de 16 por ciento con neumoperitoneo solo y 28.5 por ciento después de agregar el machacamiento del frénico o sea que el machacamiento causó un aumento de la relajación vertical de cerca de 78 por ciento.

3. En el grupo "B" de 30 enfermos que recibieron un máximo de 600 cc. cada semana la reducción apicobasal media fué de 8.4 por ciento con neumoperitoneo solo y 23.8 por ciento después de frenopraxis.

4. Cuando se usé el neumoperitoneo como único recurso el inyectar 600 cc. cada semana no produjo una elevación suficiente del diafragma. Cuando se agregó la frenopraxis se vió que aún 600 cc. semanarios proporcionaban suficiente elevación de la cúpula diafragmática paralizada sin que hubiese del lado no paralizado elevación alguna o era insignificante.

5. En once de los enfermos la parálisis del frénico de un lado fué realizada primero y el neumoperitoneo usado después. Se notó que con la parálisis frénica sola en el lado izquierdo la reducción media del diámetro apicobasal fué de 11.5 por ciento y la máxima de 23.3 por ciento. En tanto que en el lado derecho la reducción media fué de 9.3 por ciento y al máximo llegó a 13.3 por ciento. Agregando el neumoperitoneo la reducción media fué de 31.3 en el izquierdo y 32.5 por ciento en el derecho.

6. La relajación vertical producida por el neumoperitoneo o el mismo más la frenicoparálisis se distribuye entre diferentes lóbulos en diferentes proporciones dependiendo del lugar de las lesiones más grandes.

7. El neumoperitoneo combinado con frenicoparálisis aumenta ligeramente el diámetro transversal de la base del pulmón debido a desplazamiento del mediastino móvil y a los movimientos costales de compensación. Este aumento insignificante transversal de base sólo se notó cuando el mediastino era móvil y no neutralizó o perturbó los beneficios de la reducción del diámetro vertical.

RESUME

1. Une étude comparative de la réduction du diamètre apico-basal a été faite chez 62 malades, d'abord par le pneumopéritoine, et ensuite sur les mêmes malades après qu'un écrasement du phrénique eût été associé au pneumopéritoine.

2. Dans le groupe A comprenant 32 malades qui reçurent 1.000 cc d'air à intervalles de 7 à 10 jours, la réduction moyenne du diamètre apico-basal fut de 16% avec le pneumopéritoine seulement, et de 28,5% après addition de paralysie phrénique; c'est-à-dire que la paralysie phrénique créa une augmentation ultérieure de la détente verticale d'environ 78%.

3. Dans le groupe B de 30 malades qui reçurent un maximum de 600 cc d'air à intervalles d'une semaine, la réduction moyenne du diamètre apicobasal fut de 8,4% avec le pneumopéritoine seul, et 23,8% après association de la paralysie phrénique.

4. Lorsque le pneumopéritoine fut utilisé comme seul moyen de collapsus, des insufflations de 600 cc. chaque semaine ne donnèrent pas une élévation suffisante du diaphragme. Lorsque la paralysie phrénique fut associée, on constata que des insufflations de 600 cc. chaque semaine pro-

voquaient une élévation convenable de l'hémidiaphragme paralysé et pas d'élévation presque insignifiante du côté où la paralysie phrénique n'avait pas été réalisée.

5. En onze de les malades où la paralysie du phrénique d'un seul côte fut d'abord pratiquèe, et le pneumopéritoine associé ultérieurement, on nota que la paralysie phrénique seule, du côté gauche, amena une réduction moyenne du diamètre apico-basal de 11,5% et une réduction maximum de 23,3%. Du côté droit, la réduction moyenne fut de 9,3% et la réduction maximum de 13,2%. Avec l'association du pneumopéritoine, la réduction moyenne fut de 31,3% du côté gauche, et de 32,5% du côté droit.

6. La détente verticale imposée par le pneumopéritoine ou le pneumopéritoine associé à la paralysie phrénique frappe les différents lobes d'une façon différente, selon la situation des lésions principales.

7. Le pneumopéritoine associé à la paralysie phrénique augmente légèrement le diamétre transversal de la base du poumon, augmentation due au déplacement d'un médiastin mobile et aux mouvements costaux compensateurs. Cette augmentation insignifiante du diamètre basal transversal n'existe que dans les cas où le médiastin est mobile, et il ne peut ni neutraliser ni diminuer les avantages résultant de la réduction du diamètre apico-basal.

ZUSAMMENFASSUNG

1. Es erfolgte eine vergleichende Untersuchung der Verminderung des apico-basalen Durchmessers an 62 Patienten, zuerst mit Pneumoperitoneum allein und später an denselben Patienten, nachdem das Pneumoperitoneum kombiniert worden war mit einer Phrenicus-Quetschung.

2. Bei der "Gruppe A" von 32 Patienten, die 1000 ccm Luft in 7- 10-tägigen Intervallen erhielten, betrug die durchschnittliche Verminderung des apico-basalen Durchmessers 16% bei Pneumoperitoneum allein und 28,5% nach Hinzufügung der Phenicus-Quetschung; das heisst, die Phrenicus-Quetschung verursachte eine weitere Zunahme der verticaler Entspannung um ungefähr 78%.

3. Bei der "Gruppe B" von 30 Patienten, die ein Maximum von 600 ccm Luft in wöchentlichen Abständen erhielten, betrug die durchschnittliche Abnahme des apico-basalen Durchmessers 8,4% mit Pneumoperitoneum allein und 23,8% nach Hinzufügung der Phrenicus-Quetschung.

4. Gelangte das Pneumoperitoneum als alleinige Kollaps-Massnahme zur Anwendung, so ergaben Nachfüllungen von 600 ccm in wöchentlichen Abständen keinen angemessenen Zwerchfellhochstand. Wurde die Phrenicus-Quetschung hinzugefügt, konnte man erkennen, dass sogar Nachfüllungen von 600 ccm in wöchentlichen Asträndén zu einem angemessenen Hochstand der gelähmten Kuppel führte und zu keinem Anstieg oder unbedeutendem Anstieg der nicht gelähmten Hälfte.

5. Bei elf Patienten wurde die Phrenicus-Lähmung auf einer Seite zuerst durchgeführt und das Pneumoperitoneum wurde später hinzugefügt. Es war zu bemerken, dass bei einer alleinigen Phrenicus-Lähmung auf der linken Seite die durchschnittliche Verminderung im apico-basalen Durchmessers 11,5% betrug und im Maximum 23,3%. Während auf der

rechten Seite die durchschnittliche Verminderung 9,3% betrug und im Maximum 13,2%. Mit der Hinzufügung des Pneumoperitoneums betrug die durchschnittliche Herabsetzung 31,3% auf der linken Seite und 32,5% auf der rechten Seite.

6. Die verticale, durch das Pneumoperitoneum oder das Pneumoperitoneum plus Phrenicus-Lähmung herbeigeführte Entspannung teilt sich in verschiedene Lappen in verschiedenem Ausmass abhängig von der Lage der hauptsächlichen Herde.

7. Das mit der Phrenicus-Lähmung kombinierte Pneumoperitoneum führt zu einer leichten Zunahme des transversalen Durchmessers der Lungenbasis infolge der Verschiebung eines beweglichen Mediastinums und kompensatorischer Rippenbewegungen. Diese unbedeutende Zunahme im transversalen basalen Durchmesser trat nur in den Fällen auf, in denen das Mediastinum beweglich war, und machte die sich aus der Verringerung des apico-basalen Durchmessers ergebenden Vorteile nicht entscheidend unwirksam oder glich sie gar aus.

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What Can Public Health Contribute to the Private Practice of Medicine?

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I deeply appreciate the honor you have paid to the Public Health Service and to me in inviting me to give the first Louis Mark Memorial Lecture.

The name of Dr. Mark is revered among public health people, as it is among all groups who are concerned with medical progress. Broadly speaking, Dr. Mark, like every great physician, was himself a public health worker in that his medical interests extended far beyond the specific needs of his own private patients. The growth of this organization, the American College of Chest Physicians, in which he was a founder and past president, is tangible evidence of his forward vision; a vision which you, who worked with him in creating and developing it, have shared.

A cynic said there are three kinds of people in this world of ours; the few who make things happen; the many who watch things happen; and the vast majority who have no idea what has happened. Dr. Mark was one of the few who made things happen. Although he was dedicated primarily to his profession and to this College, he found the time or made the time to give of his talents, energy and vision to many and varied facets of living. His philosophy of life might well be summed up in a statement he made at the age of 60: "Life has been good to me, but life is only what you make it. Many people don't learn to give, only to take. You have to give yourself and your money to enjoy life. Whatever you do, do wholeheartedly." And above all, like Abou ben Adhem, Dr. Mark loved his fellow man.

I have concluded that perhaps we can honor him most appropriately by using this time to pause from our daily labors on what has been described as the "merely urgent" and turn our attention to broader horizons—to the truly important.

It is from this viewpoint that I would like to talk to you tonight about what seems to me to be one of the most important factors of modern life: Namely, the revolutionary flow of change that has been and is still occurring in all aspects of our civilization. John Bunyan once observed "We are a part of all that we have met." If this is true, we can attribute many parts of our character, individually and as a society, to the many changes that have occurred since the turn of the century.

For example, our population has increased from 75 million in 1900 to 166 million today and is expected to reach 228 million within the next 15 years. We are no longer an agricultural economy—two-thirds of our population are now metropolitan dwellers whereas the reverse was true

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*The Surgeon General, Public Health Service, U. S. Department of Health, Education, and Welfare.

50 years ago. Moreover, our people are moving about at a tremendous rate. According to the 1950 census, more than a third of the nation's families changed address within a three year period. California's population, to cite a specific effect of such movement, increased by 18 per cent in five years. Another dramatic change is the tremendous increase in our aged population. In 1900, there were only 8 million persons over 65; today there are 14½ million and by 1975 there will probably be more than 21 million. Higher living standards, industrialization, automation, increased leisure time, television and other devices for keeping the public better informed on health are other notable changes. Health needs and problems of our people are affected greatly by these social, economic, industrial and population changes.

Medicine has been changing too. Based upon science, the profession has been profoundly influenced by the dynamic progress of science in its broadest sense. One indication of this change is the fact that over half the dramatic, therapeutic aids we use today were unknown as recently as 15 years ago.

Living in this rapidly changing environment, it is hard to see it in perspective. The changes come, month by month, year by year, and we seldom stop to consider their full import. Yet, if we are to channel change constructively, we must appraise it realistically. Too many people look at the past so much that they actually back into the future. Let us not make that mistake. Dr. Lowell T. Coggeshall in a recent address stated "We in the health professions have become too comfortable with accepted practices and must take bold steps in breaking traditions."[1]

In the health field, this means recognizing how different are the major health problems of today from those which concerned us a few years ago. Due largely to the development of preventive health practices, clinical and public health, and to the use of antibiotics in treatment, acute illnesses have ceased to be the major threat to the health of the Nation. Our number one problem now is chronic illness and disability.

This shift has profound implications for the medical and health professions. In acute illness, onset is sudden; the course of the disease is brief; and medical care from the physician, with nursing care in some instances, is all that is required. In chronic illness, by contrast, many services other than those provided by physician and nurse are needed. The situation was well described by Dr. James R. Miller, representing the American Medical Association, at the first meeting of the Commission on Chronic Illness in 1949. He said: "Time and time again, physicians have been hampered when they are confronted in the care of their patients with conditions over which they have no control . . . We recognize the lack of proper hospital facilities for the chronically ill patients, the lack of adequate nursing services both in the hospital and in the home, and the lack of facilities to help the family adjust to the changes which chronic illnesses bring about. We recognize the lack of adequate welfare funds for those who do not have sufficient savings to meet this prolonged emergency, and we appreciate the present lack of adequate facilities for rehabilitation . . . It is no longer satisfying for us to keep people alive.

Early detection and prevention are the order of the day and with early detection must be a prompt follow-up and the application of those measures which would prevent the acute disease from becoming chronic . . ."[2]

Dr. Miller's statement highlights a condition which is becoming increasingly apparent to all of us; namely, that there is no longer any definitive line dividing preventive, curative, and restorative services. In fact, these services extend even beyond the health and medical fields into wide and vaguely defined border areas of the socio-economic fields. For this reason, our traditional procedures, with each specialist working more or less independently, need to be modified.

The basic approach to chronic disease and disability must be preventive —preventing occurrence— preventing progression. We are handicapped in the former through lack of knowledge of how to prevent the occurrence of most chronic diseases. We are not so restricted in preventing the progression of disease and disability. We are failing, however, in clinical and public health practice, to utilize fully all available knowledge for preventing or delaying the progress of chronic diseases and disability.

One reason for this failure, I believe, is a lack of community planning and a resultant lack of community services to supplement and aid the practicing physician in his medical supervision of the patient.

The logical role of the public health agency in the community is to initiate such planning and to provide many of the special services required by your patients with chronic disease and disability. The team or group approach, in which physician, health official and other specialists participate, is mandatory in discharging these responsibilities. This approach implies a mutuality of respect and responsibility on the part of all persons involved. It does not mean that the physician is less important than formerly, but it does mean that the group importance is greater.

To illustrate the need for a team or group approach, let us consider the problems and needs of a woman who has hemiplegia following a cerebral accident. What happens to her? Does she stay in the hospital as long as her insurance covers the bill because, if she went home, her husband would have to stop work to care for her? Or are services available in the community to enable her, at the end of 10 days, to return home—where she will be happier—and still receive complete care under the supervision of her physician? Is rehabilitation begun during her hospital stay or is retraining neglected, as so often happens, until the acute phase of her illness is over?

In addition to medical care, such a patient obviously needs, one or even all of the following services: home nursing care, housekeeping services, physiotherapy, transportation, and training to learn to care for herself. The personnel needed to supply these restorative services includes the family physician, nurse, physical therapist, housekeeper, occupational counsellor, religious leader, family, and employer.

Similar services are needed by the tuberculosis patient, now more than ever since drug therapy has shortened his sanatorium stay. Many mental patients also, thanks to modern drug therapy, can now be cared for at home and, as you know, such patients currently occupy over half of all hospital

beds. The answer to mental health needs is not more and more hospital beds but community preventive and rehabilitative services. The aged and senile, likewise, can receive better care than is now given them, and at greatly decreased cost, if team care, supported by adequate community facilities, is available. What such an approach can do for patients crippled by accidents or arthritic disabilities is little short of miraculous—as has been demonstrated by Dr. Rusk and others who have had the advantage of practicing physical medicine in a team setting. The ever increasing cost of care of the chronically ill and disabled mandate that we find less expensive methods of care in the home whenever possible, before such rising costs affect adversely the quality of medical care. This we must not allow to happen.

Unfortunately, few communities at present are organized to cope with total health needs. A recent Public Health Service study, involving over 3,000 non-hospitalized tuberculosis patients in a national sample of rural and urban areas, revealed that almost one-fourth of the patients with active disease were receiving no known medical supervision. In over half of the cases at home, the sputum status of the patient was unknown to the health departments who were responsible for controlling the spread of the disease.

Another Public Health Service study—this one in the cancer field—revealed that there is a lag of several years between the time when cervical cancer can be detected by exfoliative cytology and the time when the appearance of ordinary symptoms prompts the victims to seek medical care. Yet the cytologic test, which detects the disease when it is almost 100 per cent curable, is not being used on a mass basis except in the six or seven communities where the Public Health Service is extending its studies of the test as a casefinding technique. To take maximum advantage of the potential of exfoliative cytology, a tremendous job of health education and of organizing community services would have to be done.

I could cite many other evidences of unmet needs, and I am sure you could do the same. It all sifts down to the fact that many of our communities are better organized to cope with yesterday's major health problems than today's and that it will require group understanding, planning, and action to change this situation. We of the medical and health professions must take the lead, with sympathetic understanding and willingness to consider problems broader than our own immediate areas of interest.

A first step, obviously, is to define the problem. Here the public health approach may prove particularly helpful. Through epidemiologic studies, public health agencies have often learned how a disease can be controlled even before its etiologic agent is known. Retrolental fibroplasia, endemic goiter, and pellagra are well known examples. Similar studies have demonstrated the relationship of rubella in the first trimester of pregnancy to the occurrence of congenital heart disease in the infant, and the relationship of streptococcal infections to the subsequent development of rheumatic fever. It is quite possible that epidemiologic studies of cancer, hypertension, coronary artery disease and other chronic conditions may

prove equally lucrative.

Physicians also rely on public health services for statistical data on mortality and morbidity which are useful to them in planning research and evaluating therapy.

Along with these traditional public health studies, however, there is need for community studies on a broader scale. What are the diseases and impairments of major importance in your community? What is the nature, degree, and duration of resulting disability? What type of care is received? What additional services are needed? How can we place primary emphasis where it belongs—on home and office care—on self care and restoration?

Studies of this type, often conducted through health councils, with leadership from the medical and health professions but with the active participation of citizen groups, have many values. First of all, they establish at the start the teamwork relationship which is so essential in meeting total health needs. Second, they provide a factual basis on which a comprehensive program can be built, with first priority assured for the problems that are revealed to be most urgent. Third, because all groups concerned have participated, there is genuine understanding, cooperation and support for whatever actions are undertaken.

This approach, admittedly, is foreign to our traditional ways of working. It is much easier for the private physician to treat specific medical needs without concerning himself about other types of services his patient may need. It is much easier for the health officer to limit his program to the established routines of sanitation and communicable disease control. Voluntary health agencies have a certain understandable vested interest in restricting their activities to the specific disease entities for which they raise their funds. Yet all three groups have an overpowering incentive for breaking through these barriers—that incentive being that the division of labor system no longer works. For optimum results, physical therapy must start with medical therapy, not afterwards; planning for home care must start when hospital care begins, not when it ends. In brief, the most effective modern methods of treating most diseases and injuries require a coordinated treatment schedule. The patient can get such a schedule only if the groups involved work it out together.

Group planning and action calls, first of all, for a certain attitude of mind toward the changes that have occurred and the contributions others can make—a tolerance of ways and thoughts which are not necessarily ours; an open mind in the free spirit of science; a ready acceptance of the best from any and every source; an attitude of rational receptiveness rather than antagonism to new ideas.

These are attitudes the physician can take without losing his freedom, his initiative and his primary responsibility. Dr. Osler, in his "Essay on Books and Man," states that "in the records of no other profession is there to be found so large a number of men who have combined intellectual pre-eminence with nobility of character." If we are to maintain that reputation, we must learn to work together, recognizing that our role is not exclusive of all others; that medical progress has a definite relationship to socio-economic and other changes in our civilization.

I recognize that in stressing the need for teamwork to this audience, I am in a sense preaching to the converted. The American College of Chest Physicians has always worked closely with the Public Health Service as well as with many other groups. Your representatives have served with ours on numerous committees dealing with industrial health, air pollution research and radiological health hazards—to mention only a few. Currently, as you know, we are working together on a project that has tremendous potentialities; namely, the study of techniques for tuberculosis prophylaxis. One proposal for this was sponsored by the American College of Chest Physicians. To carry it out, the Public Health Service has contracted with the Phipps Institute to conduct a study among American Indians. Through this and other work, there is good reason to believe that we may know within the next three years whether isoniazid is as effective in preventing tuberculosis in humans as our animal experiments have led us to hope it may be.

This project is a good illustration of constructive use of governmental resources by private groups and individuals. Other examples could be found in the use of hospital construction grants, research grants, fellowships and traineeships and the various other programs through which the Public Health Service is helping physicians to improve both the quality and quantity of medical care. By pointing up needs and by helping to plan programs, members of the medical profession—as individuals and through organizations such as this—contribute to the constructive use of Public Health Service resources. The same is true of the resources of State and local governments. In the last analysis, it is the quality of citizen participation that determines the value of governmental programs.

And now, if you will permit me, I would like to close with a personal plea to each of you. Will you make this first Louis Mark Memorial lecture a truly memorable event by following it up with action?

What I hope you will do when you return home and resume your practice is to make a little, informal study of each of your patients. How many delayed in seeking medical care, delays that might have been avoided by a more effective program of health education? How many are harassed with family problems that counselling or social services might allay? How many are unduly handicapped because physical therapy and other rehabilitation services were not available at the most opportune time? How many could benefit from home nursing service, housekeeping service, dietetic guidance or other services that lie beyond your ability to provide and yet have a profound effect upon restoring health?

I believe you will be surprised to find, just from a critical analysis of your own patient load, what a variety of services are necessary to provide essential and quality preventive, curative and restorative care for the chronically ill and disabled.

Once you have appraised these needs in terms of your own patients, I am confident you will want to take the further actions essential in securing and using the community services which aid and supplement the care you give your patients. It will mean giving time and personal leader-

ship; it will mean becoming increasingly active on Chapter committees of this College and of your State and local medical societies, helping them to develop, for other chronic diseases of the chest, programs comparable to those you have already developed in tuberculosis, medical research and education. It will mean working with a variety of voluntary and official agencies.

To put it bluntly, what I am saying is "go home and work harder than ever" and that is a harsh message to leave with busy men. It would be much pleasanter, for me as well as for you, to leave you happily resting on your well earned laurels. But past achievements impel us to push ahead. We are now on the threshold of the greatest era in medical history. What our predecessors did for child health in the first half of the century, we can do for adult health in the last half.

And this means that the goal toward which our profession has struggled since the days of Hippocrates is almost within reach—the goal of positive, buoyant health for young and old alike. An extra push, a final breakthrough to a new approach and we can offer mankind not only a lengthened span of life but also a lengthened span of health.

SUMMARY

Prevention of chronic disease and disability and care of long term illness are today's major health needs. These needs require not only diagnosis and medical supervision by the practicing physician but also a variety of planned and integrated community services. The physician should assume leadership in securing community awareness of need and provision for these services.

RESUMEN

La prevención de enfermedad crónica, invalidez y necesidad de cuidados en enfermedades de larga evolución son actualmente necesida des mayores en la salud. Estas necesidades requieren no tan sólo diagnóstico y vigilancia médica por el médico tratante, sino una variedad de servicios planeados por la comunidad. El médico debe asumir la conducción de actividades para lograr estos servicios en la comunidad.

RESUME

La prophylaxie des affections chroniques et de l'invalidité, le traitement des maladies de longue durée, sont les obligations majeures des problèmes sanitaires actuels. Ces besoins nécessitent non seulement le diagnostic et le contrôle médical du médecin traitant, mais aussi de multiples services publics parfaitement organisés. Le médecin devrait en assumer la direction et attirer l'attention des pouvoir publics sur la nécessité de leur parfait équipement.

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Concerning a Case of Capillary Hemangioma of the Lung

CARLOS J. MAGRI, M.D., F.C.C.P., LUIS CORACH, M.D., F.C.C.P.
Rio Cuarto, Argentina
and JULIO ESCARGUEL MALBRAN, M.DD.
Cordoba, Argentina

Among mild tumors of the lung, exist some extremely rare cases such as that of capillary hemangioma of the lung, one of which we explored surgically in 1953.

Goorwitch and Madoff[1] state that few cases of capillary hemangioma appear in the United States Pathological Register of Chest Tumors and in texts of Pathology and Chest Surgery and only in exceptional cases is any reference made to them.

Our case was a woman of 30, R.U., Argentina, married and the mother of one child, who reported because of scanty blood stained sputum. She presented no other remarkable clinical symptom.

The tuberculin test (Mantoux) that we routinely apply at the first consultation gave negative result. Subsequent laboratory tests proved normal.

FIGURE 1

X-ray film revealed a round coin-like shadow of distinct edge, about 2 cms. in diameter, in the middle of the right hemithorax. (Figure 1.) This together with her past environment suggested possible hydatid cyst, and in July 1953, thoracotomy was done. The pleura was free. In the middle lobe was a pale pink nodule about the size of a walnut without umbilication of the surrounding parenchyma. When a puncture test of the tumor proved it was not a hydatid cyst, and being superficial, it was enucleated.

Histology: (Dr. Escarguel Malbrán, Fig. 2) Macroscopically the tumor was the size of a hazel-nut of brownish color and on squeezing blood emanated. Microscopically the tumor was made up of capillary interlaced some of which presented swollen endothelium. We discovered lymphocytes, eosinophilous and histiocytes in the tumor. Diagnosis: Capillary angioma.

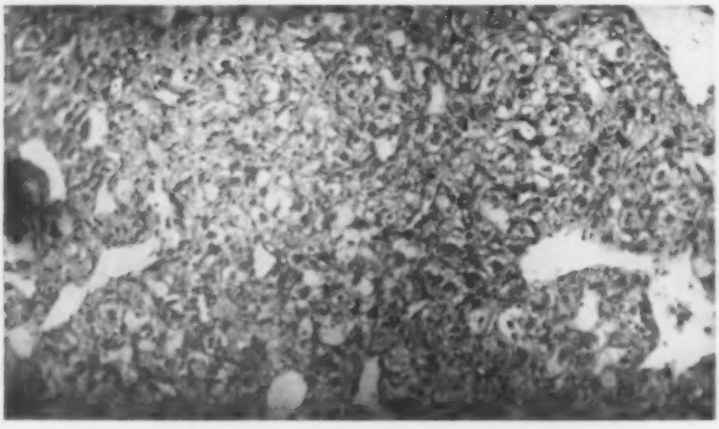

FIGURE 2

Remarks

We present this case as we think that this type of tumor may be of interest. The criticism that may be made of our handling of the case is in the surgical procedure not having made a wider resection without previously knowing the nature of the tumor.

On the other hand, we are quite aware that all solitary asymptomatic tumors of the lung discovered should be explored since the only certain diagnosis is by biopsy. Others are guess-work.

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The President's Page

To the Members of the American College of Chest Physicians:

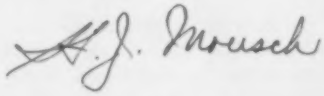
It is the responsibility of members of the medical profession to care for the sick, to advance medical knowledge and to enlighten the public on health problems. It is essential that methods be available whereby these ends can be accomplished. The public and our associates must be informed of our activities and problems, yet at the same time we must learn as much as possible concerning the interests of our communities. It is not enough that we pay only lip service to such ideals. A passive attitude will lead only to an end to progress. If we fail in our responsibility, not only will we be ignored by our neighbors, but we also will do irreparable damage to the interests of all.

There are those in the medical profession so motivated by the ideals of public service that they will gladly volunteer for their full responsibility and willingly dedicate their lives to service to others. They realize that knowledge alone is not the great objective of life, but that knowledge must be associated with action. They are not satisfied to live in tranquil contentment with the accomplishments of the past, for they are aware that the perpetuation of medicine, of which they are a part, is dependent upon progress.

There are, fortunately, only a few physicians who are unwilling to contribute to the crusade against disease. While these may repose contentedly upon their imaginary pedestals, with inflated ego and fancied superiority, they are unaware that they are depriving themselves both of a very real joy of living and of the respect of their fellow workers. Happily, however, in most cases, the failure to participate in progressive activities is due to lack of opportunity, time or knowledge of how to approach the problem.

The American College of Chest Physicians has long been dedicated to the highest ideals of medicine, and is most anxious to assist its members to achieve the sense of accomplishment which the fulfillment of these ideals confers. Participation in the annual meetings and postgraduate courses is always a stimulating challenge. All members are urged to take part in the activities of the organization, because the success, security and the future of the College rest squarely on what the individual members do. The College has realistically provided many opportunities for its members to take active parts in its work. The active co-operation of members in the meetings and in committee work provides its own recompense in the form of advancing the participant's knowledge of medicine and in helping him to acquire a better understanding of the many problems that face medicine and the College. The friendships that are formed by means of such contacts also will prove fruitful and often invaluable.

Anyone who contemplates the accomplishments of medicine thus far and speculates upon what can be done in the future by the collective intelligence and diligence of all, inevitably must reach the conclusion that the prospect is an attractive challenge. You and the American College of Chest Physicians should and can play an important role in this future. The success attained, so far as the College is concerned, will depend upon the extent to which each and every one of us contributes. Your officers are at all times most eager to receive your suggestions as to how the College can best assist in the achievement of its aims.



23rd ANNUAL MEETING OF THE COLLEGE

The Committee on Scientific Program for the 23rd Annual Meeting of the American College of Chest Physicians has announced that the preliminary scientific program will be available for publication in the March issue of *Diseases of the Chest*. The annual meeting of the College will be held at the Hotel Commodore, New York City, May 29 through June 2, 1957.

The members of the committee have devoted a great deal of time and effort to the organization of an outstanding scientific session. Dr. Karl H. Pfuetze, Chicago, chairman of the committee, reports that the very popular Fireside Conferences and Round Table Luncheon Discussions will be included in the program, as well as symposia and panel discussions of various timely subjects concerned with diseases of the heart and lungs. A clinical x-ray conference and an EKG conference are also planned. This year emphasis is being placed on papers dealing with recent clinical research projects, to which several sessions will be devoted.

Nearly one hundred requests for places on the program were received by the committee and it is regrettable that all of this excellent material could not be included. The committee wishes to express its appreciation to all physicians who submitted abstracts of their papers.

It is suggested that members who plan to attend the annual meeting in New York City should make immediate application for reservations at the Hotel Commodore. A form for this purpose may be found on page xiv in this issue of the journal.

MOTION PICTURE PROGRAM FOR ANNUAL COLLEGE MEETING

The program of films dealing with diseases of the chest to be presented at the 23rd Annual Meeting of the American College of Chest Physicians, is now being arranged by the Committee on Motion Pictures. Film sessions will be held each morning and afternoon on Friday, Saturday and Sunday, May 31, June 1 and June 2, at the Hotel Commodore, New York City.

Physicians interested in presenting films in this program are invited to send all pertinent information, i.e., brief description, color or black and white, silent or sound, running time, etc. to Dr. Paul H. Holinger, Chairman, Committee on Motion Pictures, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, for consideration by the committee.

A directory of approved films concerned with diseases of the chest (heart and/or lungs), is now in preparation by the committee. Physicians are invited to send their films for review and those approved will be listed in the new directory. Film Data Forms are available upon request.

The committee will appreciate receiving information about new films of interest to members of the American College of Chest Physicians which may be in preparation at their hospitals, clinics or medical schools.

COMMITTEE ON NOMINATIONS

Elections for offices which will expire in June, 1957, will be held at the Hotel Commodore, New York City, on Saturday, June 1. Recommendations for elective offices may be addressed to the chairman of the Committee on Nominations, Dr. Edward A. Greco, 12 Pine Street, Portland, Maine. The other members of the committee are Dr. William E. Adams, Chicago, Illinois and Dr. Arnold S. Anderson, St. Petersburg, Florida.

NEWS NOTES

Dr. Andrew L. Banyai, Milwaukee, Wisconsin, Past President of the College and Chairman of the Council on International Affairs, was awarded a scroll and key by Marquette University School of Medicine in recognition of 25 years of service as a member of the teaching faculty.

New officers of the Southern Thoracic Surgical Association, elected in December, are the following Fellows of the College: **Duane Carr,** Memphis, Tennessee, President; **DeWitt C. Daughtry,** Miami, Florida, Vice President; **Hawley H. Seiler,** Tampa, Florida, Secretary-Treasurer.

The Second Inter-American Medical Convention will be held at the Hotel El Panama, Panama City, Republic of Panama, April 3-5, 1957, under the sponsorship of the Medical Society of the Isthmian Canal Zone, a chapter of the American Medical Association.

Members of the College participating in the scientific program are Dr. Irving J. Selikoff, Paterson, New Jersey, who will speak on "Tuberculosis—Therapy and Trends"; Dr. William F. Rienhoff, Jr., of Baltimore, Maryland, who will present a lecture on "Surgery in Carcinoma of the Lung", and Dr. Hawley H. Seiler, Tampa, Florida, who will talk on "Surgery of Pulmonary Lesions Other than Cancer."

Complete information regarding the meeting may be obtained from Dr. William T. Bailey, Chairman of the Convention Executive Committee, Box O, Ancon, Canal Zone.

3rd POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The Council on Postgraduate Medical Education and the New Jersey Chapter of the College will present the 3rd Postgraduate Course on Diseases of the Chest at the Essex House Hotel, Newark, New Jersey, March 6, 13, 20, and 27 (four consecutive Wednesday afternoons). Cardiovascular Clinics will be held at St. Michael's Hospital, Newark, the 13th and 20th, 10:30 a.m.—12 noon. The tuition fee is $35 and applications should be forwarded to Dr. A. A. Peckman, 2511 Hudson Boulevard, Jersey City 4, New Jersey, Chairman of the committee. Other members of the committee are Drs. David T. DuBow, Manville; James S. D. Eisenhower, Jr., Wildwood; and Adrian M. Sabety, East Orange. Following is the schedule of instruction:

Wednesday, March 6

Pulmonary Tuberculosis—Home and Hospital Care
"Medical Treatment"
Martin J. Sokoloff, Philadelphia, Pennsylvania
"Surgical Treatment"
J. Maxwell Chamberlain, New York, New York
"Management of Bronchopulmonary Infections"
David Ulmar, New York, New York
"Pulmonary Manifestations of Collagen Diseases"
Eli H. Rubin, Bronx, New York
"Preliminary Aspects of Fungus Diseases"
Alvis E. Greer, Houston, Texas
Panel on Occupational Diseases of the Lung
Moderator: Joseph A. Smith, Glen Gardener, New Jersey
"Pulmonary Function Evaluation in Relation to Occupational Diseases"
Peter A. Theodos, Philadelphia, Pennsylvania
"Pneumoconiosis"
Leonard Greenburg, New York, New York
"The Pulmonary Aspect of Gas Diseases in Industry"
Morris Kleinfeld, New York, New York
Discussion

Wednesday, March 13

Symposium on Cardiopulmonary Disease
Moderator: Samuel Cohen, Jersey City, New Jersey
"Pulmonary Physiology in Relation to Emphysema"
George C. Leiner, East Orange, New Jersey
"Facts and Fancies in the Management of the Patient with Bronchial Asthma"
Maurice S. Segal, Boston, Massachusetts
"Methods of Bronchial Drainage in the Treatment of Bronchopulmonary Diseases"
Gustav J. Beck, New York, New York
"The Genesis and Electrophysiology of the Normal Electrocardiogram"
Simon Dack, New York, New York

Symposium on Coronary Artery Diseases
Moderator: Anthony Crecca, Newark, New Jersey
"Etiology, Diagnosis, and Prevention"
John S. LaDue, New York, New York
"Management of Acute Attack and Long Term Care"
Samuel Bellet, Philadelphia, Pennsylvania
"Surgery"
Charles P. Bailey, Philadelphia, Pennsylvania

Wednesday, March 20

Moderator: Arthur Bernstein, Newark, New Jersey
"The Management of the Hypertensive Patient"
Louis A. Soloff, Philadelphia, Pennsylvania
"Value of Left Heart Catheterization in Diagnosis and Treatment of Mitral and Aortic Valve Disease"
Harry Goldberg, Philadelphia, Pennsylvania
"Congestive Failure in Infancy"
Rachel Ash, Philadelphia, Pennsylvania
"Diagnosis and Treatment of Cardiac Arrythmias"
William I. Gefter, Philadelphia, Pennsylvania
"Clinical Fluoroscopy of Heart"
John B. Schwedel, New York, New York

Symposium on Acquired Cardiovascular Disease
Moderator: Adrian M. Sabety, East Orange, New Jersey
"Medical Aspects"
William Likoff, Philadelphia, Pennsylvania
"Surgical Aspects—Treatment of Acquired Valvular Disease"
Dwight E. Harken, Boston, Massachusetts
"Surgical Treatment of Acquired Diseases of the Aorta"
Ralph A. Deterling, New York, New York

Wednesday, March 27

Symposium on Benign and Malignant Lesions of the Thorax
Moderator: Albert A. Peckman, Jersey City
"The Challenge of Carcinoma of the Lung"
Richard H. Overholt, Boston, Massachusetts
"Etiology and Treatment of Spontaneous Pneumothorax"
Daniel A. Mulvihill, Teaneck, New Jersey
"Carcinoma of the Esophagus"
David P. Boyd, Boston, Massachusetts
"Role of Radiotherapy in the Treatment of Lung Cancer"
Bernard Roswit, New York, New York
"Chemotherapy of Lung Carcinoma"
Gordon B. Magill, New York, New York
"Thoracic Injuries"
Laurence Miscall, New York, New York
"Mediastinum"
Herbert C. Maier, New York, New York

Forum on Thoracic Surgery
Moderator: Paul Geary, Metuchen, New Jersey
Panel Discussion

POSTGRADUATE COURSE TO BE PRESENTED IN MILWAUKEE

A postgraduate course on diseases of the chest will be presented in Milwaukee, by the Wisconsin Chapter of the College and the Marquette University School of Medicine under the sponsorship of the Council on Postgraduate Medical Education of the American College of Chest Physicians. The program will be presented on four Wednesday mornings, March 6, 13, 20 and 27, at the Milwaukee County General Hospital and the Veterans Administration Hospital, at Wood, Wisconsin. Tuition fee for the course is $25.00 payable to Marquette University School of Medicine, 561 North Fifteenth Street, Milwaukee 3, Wisconsin. The course has been allotted 12 hours of formal postgraduate study credits by the Wisconsin Academy of General Practice.

Dr. Francis D. Murphy, Clinical Professor and Director of the Department of Medicine, Marquette University School of Medicine, is Honorary Chairman of the postgraduate course. The Director is Dr. Mischa J. Lustok, Assistant Clinical Professor of Medicine, and Drs. Howard L. Correll and George A. Hellmuth, Associate Professors of Medicine, are Co-Directors.

Schedule of Instruction

March 6 —Milwaukee County General Hospital
Chairman: Mischa J. Lustok, Milwaukee, Wisconsin
9 a.m. Introductory Remarks
Francis D. Murphy, Milwaukee, Wisconsin
Clinic on Rheumatic Heart Disease
George A. Hellmuth, Milwaukee, Wisconsin
Clinic on Cardiac Arrhythmias
Richard Langendorf, Chicago, Illinois
Panel Discussion: Mischa J. Lustok, *Moderator*, George A. Hellmuth, John H. Huston and Richard Langendorf

March 13—Veterans Administration Hospital
Chairman: Roger A. Hemphill, Milwaukee
9 a.m. Introductory Remarks
Mark W. Garry, Milwaukee
Clinic on Pulmonary Diseases
Arthur M. Olsen, Rochester, Minnesota
Clinic on Allergic Diseases of the Lungs
John M. Sheldon, Ann Arbor, Michigan
Panel Discussion: Roger A. Hemphill, *Moderator*, Ross C. Kory, Arthur M. Olsen and John M. Sheldon

March 20—Veterans Administration Hospital
Chairman: Howard L. Correll, Milwaukee
9 a.m. Clinic on Congestive Heart Failure
Wright R. Adams, Chicago, Illinois
Clinic on Hypertension
George E. Wakerlin, Chicago, Illinois
Panel Discussion: Howard L. Correll, *Moderator*, Wright R. Adams, Ross C. Kory, Theodore J. Pfeffer and George E. Wakerlin

March 27—Milwaukee County General Hospital
Chairman: George A. Hellmuth, Milwaukee
9 a.m. Clinic on Coronary Heart Disease
Walter S. Priest, Chicago, Illinois
Clinic on Cardiac Surgery
John W. Kirklin, Rochester, Minnesota
Panel Discussion: George A. Hellmuth, *Moderator*, John H. Huston, John W. Kirklin and Walter S. Priest

There will be no formal lectures. Each clinic will be a "wet" clinic with two patients chosen by the co-directors of each session for presentation, illustrative of the general subject assigned to the clinic. The general format of "grand rounds" will be used. A resident will present a brief resume of the case, and the pertinent evidence. The guest speaker will then discuss the case and comment on the general subject. Panel discussions will be guided along the subjects of the day. The audience will be encouraged to submit written questions.

XI CONGRESS OF ULAST

The Union of Latin American Tuberculosis Societies (ULAST) will hold its XI Congress at Medellin, Colombia, April 28-May 3, 1957. Dr. Rafael J. Mejia, Governor of the American College of Chest Physicians for Colombia, is the President of the Congress and Dr. Carlos Arboleda Diaz, Regent of the College, is the Vice-President.

The Council on Pan American Affairs of the American College of Chest Physicians will hold a breakfast meeting during the Congress on Wednesday morning, May 1. All members of the College are invited to attend this meeting.

Members of the College who wish to participate in the Congress may obtain official registration forms by writing to the Executive Offices, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A.

ANNOUNCEMENTS

The Sixth International Congress of Otolaryngology will be held in Washington, D.C., May 5-10, 1957. Subjects to be presented are: Chronic Suppuration of the Temporal Bone; Collagen Disorders of the Respiratory Tract; Papilloma of the Larynx, in addition to papers on various phases of laryngology, rhinology, otology, and bronchoesophagology. The four official languages of the Congress are English, French, German and Spanish.

Those wishing to register should communicate with the General Secretary, Dr. Paul H. Holinger, 700 North Michigan Avenue, Chicago 11, Illinois. Applications for hotel accommodations will be sent as soon as registration is completed.

The Thoracic Center of the University of Groningen (Netherlands) will present the Sixth International Postgraduate Course in Fundamentals of Thoracic Clinical Science and Surgery May 27-June 15, 1957. Prof. L. D. Eerland is President, and Prof. R. Brinkman serves as Secretary.

The Department of Laryngology and Bronchoesophagology, Temple University Hospital and School of Medicine, will present the following postgraduate courses during 1957:

Bronchoesophagology	Laryngology and Laryngeal Surgery
February 11-22	March 11-22
May 20-31	November 4-15
September 9-20	

These courses will be given under the direction of Drs. Chevalier L. Jackson and Charles M. Norris. The tuition fee for each course is $250. Further information and application forms may be obtained from Dr. Jackson, 3401 North Broad Street, Philadelphia 40, Pennsylvania.

NEW JERSEY CHAPTER

The New Jersey Chapter met on December 12 at St. Michael's Hospital, Newark, and a symposium on "Problems in Cardiac Surgery" was presented.

The chapter will present a postgraduate course on diseases of the chest at the Essex House Hotel, Newark on the afternoons of March 6, 13, 20, and 27, with morning cardiovascular clinics at St. Michael's Hospital on March 13 and 20. The Third Selman Waksman Lecture will be given at the Hotel Essex House on March 27 at a dinner meeting.

The annual meeting of the chapter will be held on the afternoon of May 1 at the Hadden Hall Hotel, Atlantic City, at which time new officers will be elected. The chapter will present the chest section in the scientific program for the meeting of the Medical Society of New Jersey the morning of May 1.

NEW ENGLAND STATES CHAPTER

Dr. Ralph D. Alley of Albany, New York, will address the monthly meeting of the New England States Chapter on February 20 at the New England Deaconess Hospital, Boston. Dr. Alley's subject is "Surgery of the Thoracic Aorta." Dr. Julia M. Jones, New York City, spoke on "Home and Clinic Care of Tuberculosis" at the January 16 meeting of the chapter.

MEDICAL SERVICE BUREAU

POSITION WANTED

F. C. C. P., 42 years of age, 15 years of experience in chest diseases (mainly tuberculosis), formerly medical director of a 225-bed sanatorium, ward experience, Illinois and Michigan licenses, desires relocation as staff physician. Prefers midwest or south. Minor thoracic surgery. Please address inquiries to Box 287B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Full-time staff physician wanted for the Idaho State Tuberculosis Hospital, Gooding, Idaho. New, fully equipped, modern hospital building nearing completion to replace several small antiquated units, bringing the total bed capacity to 100-120 beds. Salary governed by training and experience. Apply: Medical Director, Idaho State Tuberculosis Hospital, Gooding, Idaho.

Assistant medical director wanted for Mineral Springs Sanatorium, Cannon Falls, Minnesota, a 100-bed county tuberculosis hospital with active medical, surgical, out-patient, and investigative programs. Salary determined by experience. Furnished house and utilities supplied. Applicant must be male graduate of approved U. S. or Canadian medical school and eligible for Minnesota license. Address E. V. Bridge, M.D., Superintendent.

Staff physician wanted for a 215-bed tuberculosis hospital. Single man. Modern facilities, salary $6,000 per annum, living quarters and laundry. Must be graduate of approved school. Contact E. W. Hainlen, M.D., Director of Medical Services, Emily P. Bissell Sanatorium, 3000 Newport Gap Pike, Wilmington 8, Delaware.

Associate medical director wanted for 100-bed tuberculosis hospital. North American graduate, salary $8,500-$9,500, complete maintenance. Apply Medical Director and Superintendent, District I Tuberculosis Hospital, Madisonville, Kentucky, or State Tuberculosis Hospital Commission, New State Office Building, Frankfort, Kentucky.

CALENDAR OF EVENTS

NATIONAL MEETING

23rd Annual Meeting, American College of Chest Physicians
Hotel Commodore, New York City, May 29-June 2, 1957

POSTGRADUATE COURSES

Postgraduate Course on Diseases of the Chest
St. Francis Hotel, San Francisco, California, February 25-March 1

3rd Postgraduate Course on Diseases of the Chest
Newark, New Jersey, March 6, 13, 20, 27

Postgraduate Course on Diseases of the Chest
Milwaukee, Wisconsin, March 6, 13, 20, 27

10th Annual Postgraduate Course on Diseases of the Chest
Bellevue-Stratford Hotel, Philadelphia, April 1-5

CHAPTER MEETINGS

Clinical Session, New York State Chapter
New York City, February 22-23

Illinois Chapter, Chicago, February 19

New England States Chapter, Boston, February 20

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James Kieran, M.D., Oakland
Robert Stone, M.D., Oakland
William B. Leftwich, M.D., Oakland

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Forty-second Session

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In June 1957

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Clinical Facilities Available: Ray Brook State Tuberculosis Hospital, Will Rogers Memorial, Sanatorium Gabriels, V. A. Hospital at Sunmount, N. Y., and the General Hospital of Saranac Lake (chiefly surgical).

Research Facilities Available: Saranac Laboratory; Trudeau Laboratory; Ray Brook State Tuberculosis Hospital Laboratory and the X-Ray Laboratories of the Ray Brook State Tuberculosis Hospital and the V. A. Hospital at Sunmount.

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Students Participate Actively in the study and discussion of cases.

Fee for Three Weeks' Course is $100.00. The class is limited, therefore early application is advised. A few scholarships are available.

Certificate: A certificate of attendance is awarded to all students who complete the course.

Note: The Trudeau School is supported by grant from the Lillia Babbitt Hyde Foundation, New York, N. Y.

For Schedule and other information write to

Secretary, Trudeau School of Tuberculosis, Box 500,
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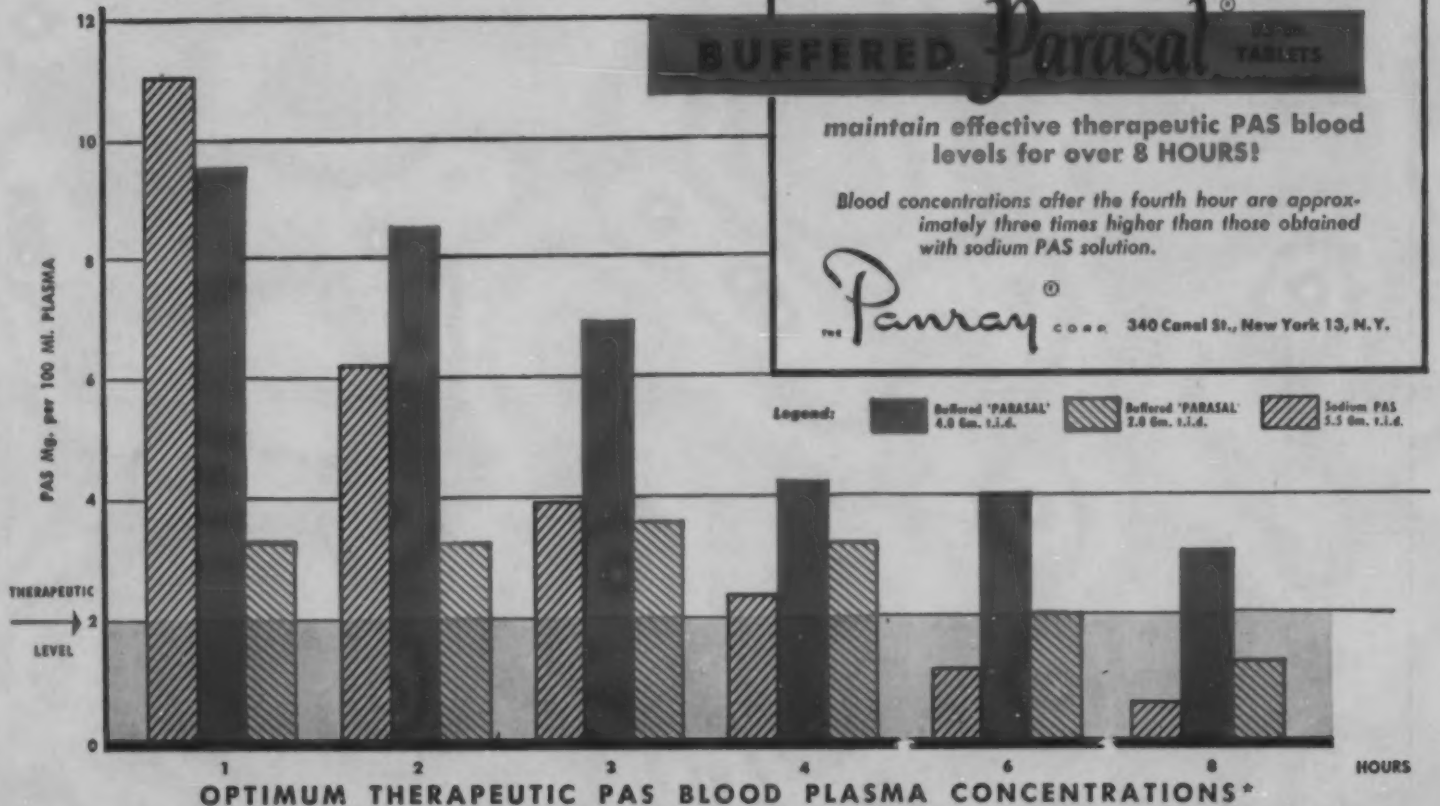

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